

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
24 March 2005 (24.03.2005)

PCT

(10) International Publication Number
WO 2005/026157 A1

(51) International Patent Classification⁷: **C07D 403/12, 401/12, 401/14, A61K 31/517, A61P 35/00 // (C07D 403/12, 239:00, 211:00) (C07D 401/12, 239:00, 205:00) (C07D 401/12, 239:00, 207:00) (C07D 401/14, 239:00, 207:00, 207:00)**

AstraZeneca R & D Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: ASTRAZENECA; Global Intellectual Property, S-151 85 Sodertalje (SE).

(21) International Application Number:
PCT/GB2004/003915

(22) International Filing Date:
13 September 2004 (13.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0321621.5 16 September 2003 (16.09.2003) GB
0406160.2 19 March 2004 (19.03.2004) GB

(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; Sodertalje, S-151 85 (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HENNEQUIN, Laurent, Francois, Andre [FR/FR]; AstraZeneca Pharma, Z.I. la Pompelle, BP 1050, F-51689 Reims (FR). HALSALL, Christopher, Thomas [GB/GB];

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

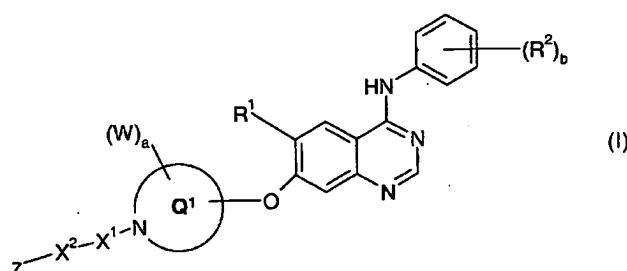
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINE DERIVATIVES



(57) Abstract: The invention concerns quinazoline derivatives of the Formula (I); wherein each of R¹, R², W, X¹, X², Z, a and b are as defined in the description; processes for their preparation; pharmaceutical compositions containing them and their use in the manufacture of a medicament for providing an anti-proliferative effect. The quinazoline derivatives of Formula (I) are expected to be useful in the treatment of diseases such as certain cancers mediated by erbB receptor tyrosine kinases, particularly EGFR tyrosine kinase.

WO 2005/026157 A1

QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically acceptable salts, or pharmaceutically acceptable esters thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The 5 invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

- Many of the current treatment regimes for diseases resulting from the abnormal 10 regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents are currently being developed, for example selective inhibitors of cell signalling pathways.
- 15 These types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide 20 variety of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the intracellular signalling pathways, therefore transducing the signal across the plasma membrane and 25 allowing the individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As 30 phosphorylation is such an important regulatory mechanism in the signal transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in abnormal cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, *Biochimica et Biophysica Acta*, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, *Oncogene*, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye *et al*, *EMBO J.*, 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper *et al*, *Adv. Cancer Res.*, 2000, 77, 25) such as breast cancer (Sainsbury *et al*, *Brit. J. Cancer*, 1988, 58, 458; Guerin *et al*, *Oncogene Res.*, 1988, 3, 21; Slamon *et al*, *Science*, 1989, 244, 707; Klijn *et al*, *Breast Cancer Res. Treat.*, 1994, 29, 73) and reviewed in Salomon *et al*, *Crit. Rev. Oncol. Hematol.*, 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al*, *Brit. J. Cancer*, 1986, 54, 265; Reubi *et al*, *Int. J. Cancer*, 1990, 45, 269; Rusch *et al*, *Cancer Research*, 1993, 53, 2379; Brabender *et al*, *Clin. Cancer Res.*, 2001, 7, 1850) as well as other cancers of the lung

(Hendler *et al.*, Cancer Cells, 1989, 7, 347; Ohsaki *et al.*, Oncol. Rep., 2000, 7, 603), bladder cancer (Neal *et al.*, Lancet, 1985, 366; Chow *et al.*, Clin. Cancer Res., 2001, 7, 1957, Zhau *et al.*, Mol Carcinog., 3, 254), oesophageal cancer (Mukaida *et al.*, Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, Oncogene Res., 1987, 1, 149; Kapitanovic *et al.*, Gastroenterology, 2000, 112, 1103; Ross *et al.*, Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, Histochem. J., 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, J. Natl. Cancer Inst., 2000, 92, 1866); leukaemia (Konaka *et al.*, Cell, 1984, 37, 1035, Martin-Subero *et al.*, Cancer Genet Cytogenet., 2001, 127, 174), ovarian (Hellstrom *et al.*, Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, Neoplasma, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors, it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender *et al.*, Clin. Cancer Res., 2001, 7, 1850; Ross *et al.*, Cancer Investigation, 2001, 19, 554, Yu *et al.*, Bioessays, 2000, 22, 7, 673). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn *et al.*, Oncogene, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.*, Science, 1988, 242, 933, Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al.*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565).

Recently the small molecule EGFR tyrosine kinase inhibitor, Iressa (also known as gefitinib, and ZD1834) has been approved for use in the treatment of advanced non-small cell lung cancer. Furthermore, findings using inhibitory antibodies against EGFR and erbB2

(c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al.*, 2000, Oncogene, **19**, 6550-6565).

Amplification and/or activity of members of the erbB receptor tyrosine kinases have
5 been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, **6**, 933; Elder *et al.*, Science, 1989, **243**, 811), benign prostatic hyperplasia (BPH) (Kumar *et al.*, Int. Urol. Nephrol., 2000, **32**, 73), atherosclerosis and restenosis (Bokemeyer *et al.*, Kidney Int., 2000, **58**, 549). It is therefore expected that inhibitors of erbB receptor tyrosine kinases will be
10 useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

European patent application EP 566 226 discloses certain 4-anilinoquinazolines that are receptor tyrosine kinase inhibitors.

International patent applications WO 96/33977, WO 96/33978, WO 96/33979, WO
15 96/33980, WO 96/33981, WO 97/30034, WO 97/38994 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position and a substituent at the 6- and/or 7- position possess receptor tyrosine kinase inhibitory activity.

European patent application EP 837 063 discloses aryl substituted 4-aminoquinazoline derivatives carrying moiety containing an aryl or heteroaryl group at the 6-or 7- position on
20 the quinazoline ring. The compounds are stated to be useful for treating hyperproliferative disorders.

International patent applications WO 97/30035 and WO 98/13354 disclose certain 4-anilinoquinazolines substituted at the 7- position are vascular endothelial growth factor receptor tyrosine kinase inhibitors.

25 WO 00/55141 discloses 6,7-substituted 4-anilinoquinazoline compounds characterised in that the substituents at the 6-and/or 7-position carry certain ester groups.

WO 00/56720 discloses 6,7-dialkoxy-4-anilinoquinazoline compounds for the treatment of cancer or allergic reactions.

WO 01/21596 discloses the use of certain 4-anilinoquinazoline derivatives as aurora 2
30 kinase inhibitors.

WO 02/18351 and WO 02/18372 disclose certain 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position which are stated to have an inhibitory effect upon signal transduction mediated by tyrosine kinases.

WO 02/41882 discloses 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position by a substituted pyrrolidinyl-alkoxy or piperidinyl-alkoxy group.

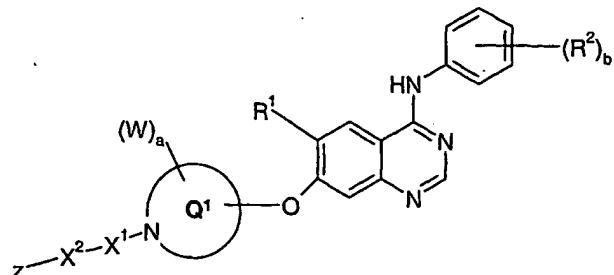
We have now found that surprisingly certain quinazoline derivatives substituted at the 7-position with a substituent containing certain optionally substituted alkanoyl or sulfonyl groups possess potent anti-tumour activity. The compounds of the present invention also possess good cellular potency, and favourable physical properties, particularly solubility, which may provide advantages in the formulation and delivery of the compound to patients. Some of the compounds of the invention posses favourable DMPK properties, for example high bioavailability and/or high free-plasma levels and/or advantageous half life and/or advantageous volume of distribution and such properties are expected to provide improved in-vivo efficacy and may reduce inter-patient variability in exposure to the compound compared to other EGFR tyrosine kinase inhibitors such as gefitinib.

Furthermore, many of the compounds according to the present invention are inactive or only weakly active in a hERG assay.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of EGF receptor tyrosine kinase.

Generally the compounds of the present invention possess potent inhibitory activity against the erbB receptor tyrosine kinase family, for example by inhibition of EGF and/or erbB2 and/or erbB4 receptor tyrosine kinases, whilst possessing less potent inhibitory activity against other kinases, such as VEGF and KDR receptor tyrosine kinases. Furthermore, the compounds of the present invention possess substantially better potency against the EGFR tyrosine kinase over that of the erbB2 tyrosine kinase. Accordingly, it may be possible to administer a compound according to the present invention at a dose that is sufficient to inhibit EGFR tyrosine kinase whilst having no significant effect upon erbB2 (or other) tyrosine kinases. The selective inhibition provided by the compounds according to the present invention may provide treatments for conditions mediated by EGFR tyrosine kinase, whilst reducing undesirable side effects that may be associated with the inhibition of other tyrosine kinases.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula I:



I

5 wherein:

R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl,

10 (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R^3), CO, CH(OR³), CON(R^3), N(R^3)CO, SO₂N(R^3), N(R^3)SO₂, CH=CH and

15 C≡C wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or

20 from a group of the formula :

$$Q^3-X^4-$$

wherein X^4 is a direct bond or is selected from CO and N(R^4)CO, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R^1 substituent, other than a CH₂ group

25 within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio,

(1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl,

- 5 N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, C(R⁵)₂O, C(R⁵)₂S and C(R⁵)₂N(R⁵), wherein R⁵ is

- 10 hydrogen or (1-6C)alkyl, and Q⁴ is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl; (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different, selected from

- 15 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, sulfamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl,
- 20 N,N-di-[(1-6C)alkyl]sulfamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

$-X^6-R^6$

- 25 wherein X⁶ is a direct bond or is selected from O, N(R⁷) and C(O), wherein R⁷ is hydrogen or (1-6C)alkyl, and R⁶ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
- 30 carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo or thioxo substituents;

b is 1, 2, 3, 4 or 5;

- each R², which may be the same or different, is selected from halogeno, cyano, nitro, 5 hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, 10 N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino and a group of the formula:

-X⁷-R⁸

- wherein X⁷ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, 15 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl;

- Q¹ is a 4, 5, 6 or 7 membered saturated or partially unsaturated monocyclic heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional 20 heteroatoms selected from O, S and N, and which ring is linked to the oxygen atom in Formula I by a ring carbon;

a is 0, 1, 2, 3 or 4;

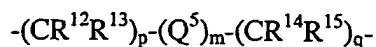
- each W, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, oxo, amino, formyl, mercapto, (1-6C)alkyl, 25 (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

-X⁸-R¹⁰

- wherein X⁸ is a direct bond or is selected from O, CO, SO₂ and N(R¹¹), wherein R¹¹ is hydrogen or (1-6C)alkyl, and R¹⁰ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, 30 (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl or N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl;

X¹ is selected from CO and SO₂;

X² is a group of the formula:



wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R¹², R¹³, R¹⁴ and R¹⁵, which may be the same or different, is selected from

hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q⁵ is

5 selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydrogen, hydroxy, amino, (1-6C)alkylamino,

10 di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino,

N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:



wherein X⁹ is a direct bond or is selected from O, N(R¹⁶), SO₂ and SO₂N(R¹⁶),

wherein R¹⁶ is hydrogen or (1-6C)alkyl, and Q⁶ is (3-7C)cycloalkyl,

15 (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl,

heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X⁹ is a direct bond, Q⁶ is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent

20 are optionally separated by the insertion into the chain of a group selected from O, S, SO,

SO₂, N(R¹⁷), CO, -C=C- and -C≡C- wherein R¹⁷ is hydrogen or (1-6C)alkyl,

and wherein and wherein any CH₂ or CH₃ group within any Z group, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino,

25 carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,

(1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,

(2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,

N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and

30 N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z-substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl,

(2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$-X^{10}-R^{18}$

5 wherein X^{10} is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl,
and wherein any heterocyclyl group within a Z substituent optionally bears 1 or 2 oxo
10 substituents, provided that said oxo substituent(s) is not on a ring carbon which is adjacent to a ring oxygen in the heterocyclyl group;
provided that:

(i) when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino, R¹ is hydrogen or (1-3C)alkoxy, and X¹ is CO, then a is 0 and Z is selected
15 from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q⁶-X⁹-; and
(ii) when Q¹ is piperidinyl, Z is hydrogen;
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

20 According to another aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof wherein R¹, R², W, X¹, X², a and b are as hereinbefore defined; and

 Z is selected from hydrogen, hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino,
25 N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

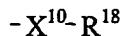
Q⁶-X⁹-

 wherein X⁹ is a direct bond or is selected from O, N(R¹⁶), SO₂ and SO₂N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and Q⁶ is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl,
30 heterocyclyl or heterocyclyl-(1-4C)alkyl,
 provided that when X⁹ is a direct bond, Q⁶ is heterocyclyl,
 and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁷), CO, -C=C- and -C≡C- wherein R¹⁷ is hydrogen or (1-6C)alkyl,

- and wherein and wherein any CH₂ or CH₃ group within any Z group, other than a CH₂ group within a heterocycl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

- and wherein any heterocycl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:



- wherein X¹⁰ is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl; provided that:

- (i) when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino, R¹ is hydrogen or (1-3C)alkoxy, and X¹ is CO, then a is 0 and Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q⁶-X⁹-; and
- (ii) when Q¹ is piperidinyl, Z is hydrogen.

In a particular embodiment of the invention there is provided a quinazoline derivative of the Formula I as defined above, or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain
5 version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino,
10 cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic
15 form which possesses the above-mentioned activity. It is further to be understood that in the names of chiral compounds (*R,S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R,S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic mixture contains *R* and *S*
20 enantiomers in the ratio 50:50. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

25 Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (for example Q², Q⁴ or Q⁶) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' or R group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (for example Q², Q⁴ or Q⁶) when it is
30 (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl. It is to be understood that reference to (3-7C)cycloalkylene used herein for Q⁵ refers to a divalent (3-7C)cycloalkane linking group, which group may be linked via different carbon atoms in the (3-

7C)cycloalkylene ring, or which may be linked via a single carbon atom in the (3-7C)cycloalkylene ring. Accordingly, reference to, for example, a "cyclopropylene" group includes cycloprop-1,2-ylene and a cyclopropylidene group of the formula:



- 5 However references to an individual (3-7C)cycloalkene group such as cyclopropylidene are specific for that group only. A similar convention is adopted for the (3-7C)cycloalkenylene groups represented by Q⁵.

- A suitable value for any one of the 'Q' groups (for example Q², Q³, Q⁴ or Q⁶) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is a non-aromatic saturated 10 (i.e. ring systems with the maximum degree of saturation) or partially saturated (i.e. ring systems retaining some, but not the full, degree of unsaturation) 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, which, unless specified otherwise, may be carbon or nitrogen linked, for example oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, decahydroisoquinolinyl or decahydroquinolinyl, particularly tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,4-oxazepanyl, thiamorpholinyl 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl, more particularly tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydrothien -3-yl, tetrahydrothiopyran-4-yl, pyrrolidin-1-yl pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, morpholin-2-yl, piperidino, piperidin-4-yl, piperidin-3-yl, piperidin-2-yl or piperazin-1-yl. A nitrogen or sulphur atom within a heterocyclyl group may 25 be oxidized to give the corresponding N or S oxide, for example 1,1-dioxotetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothiopyranyl or 1-oxotetrahydrothiopyranyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.
- 30 A suitable value for Q¹ is a non-aromatic saturated or partially saturated 4 to 7 membered monocyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, provided at least one heteroatom is nitrogen, which ring is carbon linked to the

oxygen atom in Formula 1. Suitable values include, for example, those heterocyclic groups mentioned above that contain at least one nitrogen atom, for example azetidinyl, pyrrolinyl, pyrrolidinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, decahydroisoquinolinyl or decahydroquinolinyl.

- Particular values for Q¹ is a carbon linked non-aromatic 4, 5, 6 or 7 membered monocyclic heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 further heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclyl group may be fully saturated or partially saturated. More particularly Q¹ is a carbon linked 4, 5 or 6 membered monocyclic heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 further heteroatom selected from oxygen, nitrogen and sulfur, which heterocyclyl group may be partially saturated or preferably fully saturated. Still more particularly Q¹ is a carbon linked monocyclic fully saturated 4, 5 or 6 membered monocyclic heterocyclyl group containing 1 nitrogen heteroatom. Suitable values of such groups represented by Q¹ include the appropriate heterocyclyl groups listed above, more particularly azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl (all of which are linked to the oxygen atom in Formula I by a ring carbon), more particularly, azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl, and still more particularly azetidin-3-yl.

- A suitable value for a 'Q' group when it is heterocyclyl-(1-6C)alkyl is, for example, heterocyclymethyl, 2-heterocyclylethyl and 3-heterocyclylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heterocyclyl-(1-6C)alkyl group, an (3-7C)cycloalkyl-(1-6C)alkyl or (3-7C)cycloalkenyl-(1-6C)alkyl is present.

- Suitable values for any of the 'R' groups (R¹ to R¹⁹), W, or for various groups within a X¹, X² or Z group include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
30 for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenoxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;

- for (1-6C)alkylsulphanyl:
for (1-6C)alkylsulphonyl:
for (1-6C)alkylamino:
- 5 for di-[(1-6C)alkyl]amino:
for (1-6C)alkoxycarbonyl:
for N-(1-6C)alkylcarbamoyl:
- 10 for N,N-di-[(1-6C)alkyl]carbamoyl:
for (2-6C)alkanoyl:
for (2-6C)alkanoyloxy:
- 15 for (2-6C)alkanoylamino:
for N-(1-6C)alkyl-(2-6C)alkanoylamino:
for N-(1-6C)alkylsulphamoyl:
for N,N-di-[(1-6C)alkyl]sulphamoyl:
for (1-6C)alkanesulphonylamino:
- 20 for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino:
for (3-6C)alkenoylamino:
for N-(1-6C)alkyl-(3-6C)alkenoylamino:
for (3-6C)alkynoylamino:
- 25 for N-(1-6C)alkyl-(3-6C)alkynoylamino:
for amino-(1-6C)alkyl:
for (1-6C)alkylamino-(1-6C)alkyl:
- 30 for di-[(1-6C)alkyl]amino-(1-6C)alkyl:
- methylsulphanyl and ethylsulphanyl;
methylsulphonyl and ethylsulphonyl;
methylamino, ethylamino, propylamino,
isopropylamino and butylamino;
dimethylamino, diethylamino, N-ethyl-
N-methylamino and diisopropylamino;
methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl
and tert-butoxycarbonyl;
N-methylcarbamoyl, N-ethylcarbamoyl and
N-propylcarbamoyl;
N,N-dimethylcarbamoyl, N-ethyl-
N-methylcarbamoyl and N,N-diethylcarbamoyl;
acetyl, propionyl, butyryl and isobutyryl;
acetoxy and propionyloxy;
acetamido and propionamido;
N-methylacetamido and N-methylpropionamido;
N-methylsulphamoyl and N-ethylsulphamoyl;
N,N-dimethylsulphamoyl;
methanesulphonylamino and ethanesulphonylamino;
N-methylmethanesulphonylamino and
N-methylethanesulphonylamino;
acrylamido, methacrylamido and crotonamido;
N-methylacrylamido and N-methylcrotonamido;
propiolamido;
N-methylpropiolamido;
aminomethyl, 2-aminoethyl, 1-aminoethyl and
3-aminopropyl;
methylaminomethyl, ethylaminomethyl,
1-methylaminoethyl, 2-methylaminoethyl,
2-ethylaminoethyl and 3-methylaminopropyl;
dimethylaminomethyl, diethylaminomethyl,
1-dimethylaminoethyl, 2-dimethylaminoethyl and
3-dimethylaminopropyl;

- for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
- 5 for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
- 10 for (1-6C)alkylthio-(1-6C)alkyl: methylthiomethyl, ethylthiomethyl, 2-methylthioethyl, 1-methylthioethyl and 3-methylthiopropyl;
- for (1-6C)alkylsulphinyl-(1-6C)alkyl: methylsulphinylmethyl, ethylsulphinylmethyl, 2-methylsulphinylethyl, 1-methylsulphinylethyl and 3-methylsulphinylpropyl;
- 15 for (1-6C)alkylsulphonyl-(1-6C)alkyl: methylsulphonylmethyl, ethylsulphonylmethyl, 2-methylsulphonylethyl, 1-methylsulphonylethyl and 3-methylsulphonylpropyl;
- 20 for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl;
- for N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl: N-methylacetamidomethyl, 2-(N-methylacetamido)ethyl and 2-(N-methylpropionamido)ethyl;
- 25 for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylamoethyl;
- (2-6C)alkanoyloxy-(1-6C)alkyl: acetoxyethyl, 2-acetoxyethyl and 2-propionyloxyethyl;
- 30 for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoyleethyl, 2-carbamoyleethyl and 3-carbamoylpropyl;
- for (2-6C)alkanoyl-(1-6C)alkyl: acetyl methyl and 2-acetyleethyl;

for N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl,

N-ethylcarbamoylmethyl,

N-propylcarbamoylmethyl,

1-(N-methylcarbamoyl)ethyl,

5

1-(N-ethylcarbamoyl)ethyl,

2-(N-methylcarbamoyl)ethyl,

2-(N-ethylcarbamoyl)ethyl and

3-(N-methylcarbamoyl)propyl;

for N,N-di[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: N,N-dimethylcarbamoylmethyl,

10

N,N-diethylcarbamoylmethyl,

2-(N,N-dimethylcarbamoyl)ethyl, and

3-(N,N-dimethylcarbamoyl)propyl;

for sulfamoyl(1-6C)alkyl:

sulfamoylmethyl, 1-sulfamoylethyl,

2-sulfamoylethyl and 3-sulfamoylpropyl;

15 for N-(1-6C)alkylsulfamoyl(1-6C)alkyl: N-methylsulfamoylmethyl,

N-ethylsulfamoylmethyl, N-propylsulfamoylmethyl,

1-(N-methylsulfamoyl)ethyl,

2-(N-methylsulfamoyl)ethyl and

3-(N-methylsulfamoyl)propyl; and

20 for N,N di-(1-6C)alkylsulfamoyl(1-6C)alkyl: N,N-dimethylsulfamoylmethyl,

N,N-diethylsulfamoylmethyl, N

methyl,N-ethylsulfamoylmethyl, 1-(

N,N-dimethylsulfamoyl)ethyl,

1-(N,N-diethylsulfamoyl)ethyl,

2-(N,N-dimethylsulfamoyl)ethyl,

2-(N,N-diethylsulfamoyl)ethyl and

3-(N,N-dimethylsulfamoyl)propyl.

When, as defined hereinbefore Z in Formula I is a group of the formula Q^6-X^9- , and X^9 is $SO_2N(R^{16})$, the SO_2 group is attached to Q^6 and the nitrogen atom is attached to X^2 in

30 Formula I. The same convention is applied to other groups defined herein. For example when X^2 is a group of the formula $Q^5-(CR^{14}R^{15})_m$, the Q^5 group is attached to the group Z in Formula I and the $(CR^{14}R^{15})_m$ group is attached to the X^1 group in Formula I.

- As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within, for example, a R¹ substituent may be optionally separated by the insertion into the chain of a group such as O, CON(R³), N(R³) or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-nyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group. It is to be understood that the term (2-6C)alkylene chain refers to any CH₂CH₂ group (for example within R¹) and includes, for example alkylene chains within a (1-6C)alkyl, (1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkenyloxy, (2-8C)alkynyl and (2-8C)alkynyloxy group.
- 5 For example the insertion of a N(CH₃) group between the third and fourth carbon atoms in a hex-5-enyloxy group in R¹ gives rise to a 3-(N-methyl-N-allylamino)propoxy group.
- When, as defined hereinbefore, any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent such as a group of the formula Q³-X⁴- wherein X⁴ is, for example, NHCO and Q³ is a heterocyclyl-(1-6C)alkyl group, suitable R¹ substituents so formed include, for example,
- 10 N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as
N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or
N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.
- 15 When reference is made herein to a CH₂ or CH₃ group optionally bearing on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH₂ group and there are suitably 1, 2 or 3 such substituents present on each said CH₃ group.
- 20 Where reference is made herein to any CH₂ or CH₃ group optionally bearing on each said CH₂ or CH₃ group a substituent as defined herein, suitable substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, and hydroxy-substituted (2-6)alkanoyl groups such as
- 25 hydroxyacetyl, 2-hydroxypropionyl and 2-hydroxybutyryl.

30 Where reference is made herein to “any CH₂ or CH₃ group, other than a CH₂ group within a heterocyclyl group, optionally bearing a substituent”, it is to be understood that such a statement is present only to distinguish between optional substituents that may be present

- on, for example, a CH₃ group in an alkyl group from substituents that may be present on carbon atoms of a heterocyclyl group. Accordingly, it is to be understood, that this statement does not exclude other substituents being present on ring carbon atoms in a heterocyclyl group when it is stated herein that said heterocyclyl group may also optionally bear one or
- 5 more substituents. For example, if R¹ is 3-(pyrrolidin-1-yl)propoxy and herein it is stated that a CH₂ or CH₃ group within, for example, a R¹ substituent, other than a CH₂ group within a heterocyclyl group, optionally bears a hydroxy substituent, and that any heterocyclyl group within R¹ optionally bears an alkyl substituent, then the optional hydroxy substituent may be present on a CH₂ of the propoxy group to give for example a 2-hydroxy-3-(pyrrolidin-1-
- 10 yl)propoxy group. Similarly an alkyl group such as methyl may be present on the pyrrolidinyl ring to give, for example, a 3-(3-methylpyrrolidin-1-yl)propoxy group. Equally, the propoxy group may be substituted by a hydroxy group and the pyrrolidinyl ring may be substituted by a methyl group to give, for example, a 2-hydroxy-3-(3-methylpyrrolidin-1-yl)propoxy group.

For the avoidance of doubt, when W is oxo, a CH₂ in Q¹ is substituted by O to give a
15 C(O) group.

- It is to be understood that reference herein to Q¹ being, for example piperidin-4-yl refers to the attachment of the piperidine ring to the oxygen in Formula I. The piperidine ring is further substituted at the 1-position by the group Z-X²-X¹- and optionally bears one or more W substituents on one or more of the available piperidinyl ring carbon atoms.
- 20 It is to be understood that certain compounds of the Formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

It is also to be understood that certain compounds of the Formula I may exhibit
25 polymorphism, and that the invention encompasses all such forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

It is also to be understood that the invention relates to all tautomeric forms of the compounds of the Formula I forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase.

- 30 A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I

which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

- 5 The term "pharmaceutically acceptable ester" used herein refers to an ester of a quinazoline derivative of the Formula I which hydrolyses in vivo to leave the parent compound or a pharmaceutically acceptable salt thereof. An in-vivo hydrolysable ester of a quinazoline of Formula I may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound, for example the solubility. Suitable ester groups that may be
10 used in the formation of pharmaceutically acceptable ester prodrugs are well known, for example as discussed in for example:
- Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the ACS Symposium Series, and in Edward B. Roche, ed.;
Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987;
15 Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191
20 (1991);
H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

- A particular pharmaceutically acceptable ester of a quinazoline derivative of the
25 Formula I or a pharmaceutically acceptable salt thereof is, an ester formed with a carboxy or, particularly, a hydroxy group (for example when Z is hydroxy) in Formula I, which ester is hydrolysed in the human or animal body to produce the parent quinazoline of Formula I when administered to a warm blooded animal such as a human.

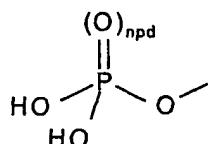
- Suitable pharmaceutically acceptable esters for a carboxy group in Formula I include
30 C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example

1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically acceptable esters for a hydroxy group in Formula I or a pharmaceutically acceptable salt thereof include inorganic esters such as phosphate esters, α -acyloxyalkyl ethers and related compounds, and esters derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms, and may be formed at any hydroxy group in the compounds of this invention, for example when Z is hydroxy or contains a hydroxy group. Following administration, the pharmaceutically acceptable ester undergoes in-vivo hydrolysis breakdown to give the parent carboxy/hydroxy group in the quinazoline derivative of Formula I.

Examples of α -acyloxyalkyl ethers that may be used to form a pharmaceutically acceptable ester include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of pharmaceutically acceptable ester forming groups for a hydroxy group in Formula I (for example when Z is hydroxy) include (1-6C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-6C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring.

Particular pharmaceutically acceptable esters are phosphate esters formed with a hydroxy group in the quinazoline derivative for the Formula I (for example when Z is hydroxy or contains a hydroxy group), or a pharmaceutically acceptable salt thereof. More particularly, pharmaceutically acceptable esters include quinazoline derivatives of the Formula I in which a hydroxy group in Formula I forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD1), or a pharmaceutically acceptable salt thereof:



(PD1)

Formula I in which a hydroxy in Formula I (for example when Z is hydroxy) forms a phosphoryl to give a group of the formula (PD1) wherein npd is 1.

Useful intermediates for the preparation of such esters include compounds containing a group of formula (PD1) in which either or both of the -OH groups in (PD1) is independently 5 protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

- Pharmaceutically acceptable esters of a quinazoline derivative of Formula I containing a group such as (PD1), may be prepared by reaction of a quinazoline derivative Formula I 10 with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection. Suitable phosphorylating agents are well known and include, for example protected phosphoramidite compounds such as a N,N-di-[(1-6C)alkyl]- phosphoramidite, for example di-tert-butyl N,N-diethylphosphoramidite.
- 15 It is to be understood that an ester group in the quinazoline derivative of the Formula I may form a pharmaceutically acceptable salt of the ester group and that such salts form part of the present invention. Where pharmaceutically acceptable salts of a pharmaceutically acceptable ester is required this is achieved by conventional techniques well known to those of ordinary skill in the art. Thus, for example, compounds containing a group of formula 20 (PD1), may ionise (partially or fully) to form salts with an appropriate number of counter-ions. By way of example, if a pharmaceutically acceptable ester pro-drug of a quinazoline derivative Formula I contains a (PD1) group, there are two HO-P- functionalities present, each of which may form an appropriate salt with a suitable counter-ion. Suitable salts of a group of the formula (PD1) are base salts such as an alkali metal salt for example sodium, an 25 alkaline earth metal salt for example calcium or magnesium or an organic amine salt for example triethylamine, or tris-(2-hydroxyethyl)amine. Thus for example the group (PD1) may form, a mono- or di-sodium salt).

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically acceptable salts, or pharmaceutically 30 acceptable esters thereof, wherein, unless otherwise stated, each of R¹, R², W, Q¹, X¹, X², a, b and Z has any of the meanings defined hereinbefore or in paragraphs (a) to (qqqq) hereinafter

- (a) R^1 is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is a direct bond or is O, and Q^2 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl,

5 heterocycl or heterocycl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1

substituent are optionally separated by the insertion into the chain of a group selected from O,

$N(R^3)$, $CON(R^3)$, $N(R^3)CO$, $CH=CH$ and $C\equiv C$ wherein R^3 is hydrogen or (1-6C)alkyl,

and wherein any $CH_2=CH$ - or $HC\equiv C$ - group within a R^1 substituent optionally bears at

10 the terminal $CH_2=$ or $HC\equiv C$ position a substituent selected from carbamoyl,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl,

(1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^3-X^4-$$

15 wherein X^4 is a direct bond or is selected from CO and $N(R^4)CO$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is heterocycl or heterocycl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocycl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano,

20 carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$ and $C(R^5)_2O$,

wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is heterocycl or heterocycl-(1-6C)alkyl,

25 and wherein any heterocycl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl,

(1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, or from a group of

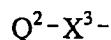
30 the formula:

$$-X^6-R^6$$

wherein X^6 is a direct bond or is selected from O and $N(R^7)$, wherein R^7 is hydrogen or (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

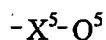
(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,
N-(1-6C)alkylcarbamoyl-(1-6C)alkyl and N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,
 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
 5 oxo substituents;

(b) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy,
 (2-6C)alkynyoxy, or from a group of the formula:



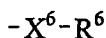
wherein X³ is a direct bond or is O, and Q² is heterocyclyl or heterocyclyl-(1-6C)alkyl,
 10 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹
 substituent are optionally separated by the insertion into the chain of a group selected from O,
 N(R³), CON(R³), N(R³)CO, CH=CH and C≡C wherein R³ is hydrogen or (1-6C)alkyl,
 and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears
 at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl,

15 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl
 and wherein any CH₂ or CH₃ group within a R¹ substituent, other than a CH₂ group
 within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more
 halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano,
 20 carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl
 and N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :



wherein X⁵ is a direct bond or is selected from O, N(R⁵), CON(R⁵), N(R⁵)CO and C(R⁵)₂O,
 wherein R⁵ is hydrogen or (1-6C)alkyl, and Q⁵ is heterocyclyl or heterocyclyl-(1-6C)alkyl,

25 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or
 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl,
 hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylsulfonyl,
 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, or from a group of the formula:



wherein X⁶ is a direct bond or is selected from O and N(R⁷), wherein R⁷ is hydrogen or
 (1-6C)alkyl, and R⁶ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

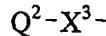
and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

- 5 (c) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R³), CON(R³), N(R³)CO, CH=CH and C≡C wherein R³ is hydrogen or (1-6C)alkyl,

- 10 and wherein any CH₂ or CH₃ group within a R¹ substituent, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl;

- 15 (d) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, or from a group of the formula :



wherein X³ is O, and Q² is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O and N(R³), wherein R³ is hydrogen or (1-4C)alkyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, cyano,

- 25 (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

- 30 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

- (e) R¹ is selected from hydroxy, (1-6C)alkoxy, or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is O, and Q^2 is azetidin-3-yl-(1-4C)alkyl, azetidin-1-yl-(2-4C)alkyl, pyrrolidin-2-yl-(1-4C)alkyl, pyrrolidin-3-yl-(1-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidin-2-yl-(1-4C)alkyl, piperidin-3-yl-(1-4C)alkyl, piperidin-4-yl-(1-4C)alkyl, piperidino-(2-4C)alkyl,

5 piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O and N(R^3), wherein R^3 is hydrogen or (1-4C)alkyl,

10 and wherein any CH₂ or CH₃ group within a R^1 substituent, other than a CH₂ group within a heterocycl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, (1-4C)alkoxy, amino, (1-4C)alkylamino and di-[(1-4C)alkyl]amino,

15 and wherein any heterocycl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkyl]carbamoyl and (2-4C)alkanoyl,

20 and wherein any heterocycl group within a substituent on R^1 optionally bears 1 oxo substituent (preferably any oxo group on a morpholino group in R^1 is located at the 3 or 5 position on the morpholino ring);

(f) R^1 is selected from hydrogen, hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy or from a group of the formula :

$$Q^2-X^3-$$

wherein X^3 is O, and Q^2 is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,

and wherein any heterocycl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, and (2-4C)alkanoyl,

30 and wherein any heterocycl group within a substituent on R^1 optionally bears 1 oxo substituent;

(g) R^1 is selected from hydrogen, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, 2-hydroxyethoxy, 2-fluoroethoxy, cyclopropylmethoxy, 2-cyclopropylethoxy, vinyloxy,

- allyloxy, ethynyoxy, 2-propynyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofurfuryloxy, tetrahydrofuran-3-ylmethoxy, 2-(tetrahydrofuran-2-yl)ethoxy, 3-(tetrahydrofuran-2-yl)propoxy, 2-(tetrahydrofuran-3-yl)ethoxy, 3-(tetrahydrofuran-3-yl)propoxy, tetrahydropyranyl methoxy,
- 5 2-tetrahydropyranylethoxy, 3-tetrahydropyranylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
- 10 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino and piperazin-1-yl,
- 15 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃),CH=CH and C≡C, and when R¹ is a vinyloxy, allyloxy, ethynyoxy or 2-propynyloxy group, the R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from
- 20 N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :
- $$Q^3-X^4-$$
- 25 wherein X⁴ is a direct bond or is NHCO or N(CH₃)CO and Q³ is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl,
- 30 piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl, and wherein any CH₂ group which is attached to 2 carbon atoms other than a CH₂ group within a heterocycl ring) or any CH₃ group which is attached to a carbon atom within

a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, ethoxy, methylsulfonyl, methylamino and dimethylamino,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,

5 trifluoromethyl, hydroxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methyl, ethyl, n-propyl, isopropyl and methoxy, and any piperidin-3-ylmethyl, piperidin-4-ylmethyl, piperazin-1-yl group within a R¹ substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypipethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetyl or propionyl,

10 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

(h) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 15 said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents, or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl and N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and 20 N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

(i) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 25 said CH₂ or CH₃ group one or more fluoro or chloro substituents, or a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

(j) R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (3-7C)cycloalkyl-oxy and (3-7C)cycloalkyl-(1-6C)alkoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ 30 substituent are optionally separated by the insertion into the chain of an O atom, and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more fluoro or chloro substituents, or a substituent selected from hydroxy and (1-4C)alkoxy;

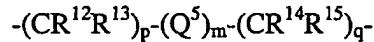
- (k) R^1 is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1
5 substituent are optionally separated by the insertion into the chain of an O atom,
and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected
from hydroxy and (1-3C)alkoxy;
- (l) R^1 is selected from hydrogen, (1-6C)alkoxy, cyclopropylmethoxy and 2-
10 cyclopropylethoxy,
and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
said CH_2 or CH_3 group one or more fluoro or chloro substituents, or a substituent selected
from hydroxy, methoxy and ethoxy;
- (m) R^1 is selected from methoxy, ethoxy, propyloxy, isopropyloxy, cyclopropylmethoxy,
15 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2,2-difluoroethoxy
2,2,2-trifluoroethoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-
piperidinoethoxy, 3-piperidinoproxy, 2-piperazinoethoxy, 3-piperazinoproxy, 2-
morpholinoethoxy and 3-morpholinoproxy;
- (n) R^1 is selected from hydrogen methoxy, ethoxy, propyloxy, isopropyloxy,
20 cyclopropylmethoxy, 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy,
2,2-difluoroethoxy and 2,2,2-trifluoroethoxy;
- (o) R^1 is selected from (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-3C)alkoxy-(2-
3C)alkoxy;
- (p) R^1 is selected from hydrogen and (1-3C)alkoxy (particularly R^1 is (1-3C)alkoxy such
25 as methoxy, ethoxy and isopropyloxy);
- (q) R^1 is hydrogen;
- (r) R^1 is methoxy;
- (s) each R^2 , which may be the same or different, is selected from halogeno, cyano, nitro,
hydroxy, amino, carboxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
30 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy, and a group of
the formula :

wherein X⁷ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl;

- 5 (t) each R², which may be the same or different, is selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;
- (u) each R², which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, hydroxy, trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl and
- 10 (1-4C)alkoxy;
- (v) each R², which may be the same or different, is selected from fluoro, chloro, bromo, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl;
- (w) each R², which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, carbamoyl, hydroxy, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, ethoxy,
- 15 vinyl, allyl, ethynyl, 1-propynyl, 2-propynyl, N-methylcarbamoyl, N-ethylcarbamoyl and N,N-dimethylcarbamoyl;
- (x) each R², which may be the same or different, is selected from fluoro, chloro, bromo, iodo, cyano, hydroxy, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, ethoxy, vinyl, allyl, ethynyl, 1-propynyl, and 2-propynyl;
- 20 (y) each R², which may be the same or different, is selected from fluoro, chloro, bromo, cyano, hydroxy, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and ethynyl;
- (z) each R², which may be the same or different, is selected from fluoro, chloro, bromo and ethynyl;
- (aa) each R², which may be the same or different, is selected from halogeno (particularly
- 25 fluoro, chloro and bromo);
- (bb) b is 1, 2 or 3 and one R² is at the meta (3-) position on the anilino group in Formula 1;
- (cc) b is 1, 2 or 3 and each R², which may be the same or different, is as defined in any of (s) to (aa) above;
- (dd) b is 1, 2 or 3, one R² is at the meta (3-) position on the anilino group in Formula 1 and
- 30 is halogeno, and when b is 2 or 3 the other R² group(s), which may be the same or different, are as defined in any of any of (s) to (aa) above;
- (ee) b is 1, 2 or 3, each R², which may be the same or different, is halogeno, and wherein one R² is at the meta (3-) position on the anilino group in Formula 1;

- (ff) b is 1 or 2, each R², which may be the same or different, is halogeno (particularly fluoro, chloro or bromo) and wherein one R² is at the meta (3-) position and the other R² is at the ortho (2-) or para (4-) position on the anilino group;
- (gg) b is 1 or 2, one R² is at the meta (3-) position on the anilino group in Formula 1 and is 5 chloro or bromo (particularly chloro) and when b is 2 the other R² group is selected from fluoro, chloro and bromo (particulalry fluoro);
- (hh) the anilino group at the 4-position on the quinazoline ring in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino and 3-ethynylanilino;
- 10 (ii) the anilino group at the 4-position on the quinazoline ring in Formula I is selected from 3-chloro-4-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino, 3-methylanilino and 3-ethynylanilino;
- (jj) the anilino group at the 4-position on the quinazoline ring in Formula I is 3-chloro-4-fluoroanilino;
- 15 (kk) the anilino group at the 4-position on the quinazoline ring in Formula I is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino (more particularly the anilino is 3-chloro-2-fluoroanilino);
- (ll) Q¹ is selected from azetidinyl, pyrrolidinyl, piperidinyl and homopiperidinyl, wherein Q¹ is carbon linked to the oxygen atom in Formula I, and provided that when Z is piperidinyl, 20 then Z is hydrogen;
- (mm) Q¹ is selected from azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, provided that when Q¹ is piperidin-3-yl or piperidin-4-yl, then Z is hydrogen;
- (nnn) Q¹ is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, provided that when Q¹ is piperidin-3-yl or piperidin-4-yl, then Z is hydrogen;
- 25 (000) Q¹ is piperidin-4-yl and Z is hydrogen;
- (ppp) Q¹ is azetidin-3-yl;
- (qqq) each W, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, oxo, (1-6C)alkyl, (1-6C)alkoxy, and from a group of the formula:
- X⁸- R¹⁰
- 30 wherein X⁸ is a direct bond or is O, and R¹⁰ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;
- (rrr) each W, which may be the same or different, is selected from halogeno, hydroxy, oxo, (1-6C)alkyl and (1-6C)alkoxy;

- (sss) each W, which may be the same or different, is selected from halogeno (particularly fluoro), hydroxy, (1-3C)alkyl and (1-3C)alkoxy;
- (ttt) a is 0, 1, or 2 and each W, which may be the same or different, is as defined in any of (qqq) to (sss);
- 5 (uuu) a is 0 or 1 and W is as defined in any of (qqq) to (sss);
- (vvv) a is 0;
- (www) Q¹ is piperidin-4-yl, a is 0 or 1, Z is hydrogen and W is as defined in any of (qqq) to (sss);
- (www) Q¹ is azetidin-3-yl, a is 0 or 1 (preferably 0) and W is (1-4C)alkyl;
- 10 (xxx) X¹ is CO;
- (yyy) X¹ is SO₂;
- (zzz) X² is a group of the formula:



wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

- 15 each of R¹², R¹³, R¹⁴ and R¹⁵, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q⁵ is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,
and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents,

- 20 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

- (aaa) X² is selected from a group of the formula -(Q⁵)_m-(CR¹⁴R¹⁵)_q- and a group of the
25 formula -(CR¹²R¹³)_q-(Q⁵)_m-, wherein m is 0 or 1, q is 1, 2, 3 or 4, and Q⁵, R¹², R¹³, R¹⁴ and R¹⁵ are as hereinbefore defined;
- (bbb) X² is a group of the formula -Q⁵-, for example (3-7C)cycloalkylene such as cyclopropylidene;
- (ccc) X² is selected from cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene,
30 methylene-(3-6C)cycloalkylene, (3-6C)cycloalkylene-methylene-, ethylene-(3-6C)cycloalkylene and (3-6C)cycloalkylene-ethylene-,

and wherein and wherein any CH₂ or CH₃ group within X², optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(ddd) X² is a group of the formula -(CR¹²R¹³)_q-,

5 q is 1, 2, 3 or 4 (particularly 1 or 2),

each of R¹² and R¹³, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

and wherein and wherein any CH₂ or CH₃ group within X², optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents,

10 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(eee) X² is a group of the formula -(CR¹²R¹³)_q-,

15 q is 1, 2 or 3,

each of R¹² and R¹³, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents,

20 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, and (1-6C)alkoxy,

(fff) X² is a group of the formula -(CR¹²R¹³)_q-(CR^{12aa}R^{13aa})-,

q is 1, 2 or 3 (particularly 1 or 2, more particularly 1),

25 each of R¹², R¹³ and R^{13aa}, which may be the same or different, is selected from hydrogen and (1-6C)alkyl,

R^{12aa} is selected from amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents,

30 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

- (ggg) X^2 is a group of the formula $-(CR^{12}R^{13})_q-$,
 q is 1, 2, 3 or 4 (particularly 1 or 2, more particularly 1),
 each of R^{12} and R^{13} , which may be the same or different, is selected from hydrogen
 and (1-6C)alkyl, provided that at least one of the R^{12} or R^{13} groups in X^2 is (1-6C)alkyl,
 5 and wherein any CH_2 or CH_3 group within an X^2 group, optionally bears on each said
 CH_2 or CH_3 group one or more halogeno substituents,
 and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group
 which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2
 or CH_3 group a substituent selected from hydroxy, and (1-6C)alkoxy;
- 10 (hhh) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,
 each of R^{12} and R^{13} , which may be the same or different, is selected from hydrogen
 and (1-6C)alkyl,
 and wherein any CH_2 or CH_3 group within X^2 , optionally bears on each said CH_2 or
- 15 CH_3 group one or more halogeno substituents,
 and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group
 which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2
 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino
 and di-[(1-6C)alkyl]amino;
- 20 (iii) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,
 each of R^{12} and R^{13} , which may be the same or different, is selected from hydrogen
 and (1-6C)alkyl, provided that at least one of R^{12} or R^{13} is a branched (1-6C)alkyl group,
 and wherein any CH_2 or CH_3 group within X^2 , optionally bears on each said CH_2 or
- 25 CH_3 group one or more halogeno substituents,
 and wherein any CH_2 group which is attached to 2 carbon atoms or any CH_3 group
 which is attached to a carbon atom within a X^2 substituent optionally bears on each said CH_2
 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino
 and di-[(1-6C)alkyl]amino;
- 30 (jjj) X^2 is selected from a group of the formula $-(CR^{12}R^{13})-$, $-(CR^{12}R^{13}CH_2)-$, $-(CR^{12}R^{13}CH_2CH_2)-$, $-(CH_2CR^{12}R^{13})-$ and $-(CH_2CH_2CR^{12}R^{13})-$,
 each of R^{12} and R^{13} , which may be the same or different, is selected from hydrogen
 and (1-6C)alkyl, provided that at least one of R^{12} or R^{13} in X^2 is a branched alkyl group,

which branched alkyl group is preferably selected from iso-propyl, iso-butyl, sec-butyl and tert-butyl,

and wherein any CH₂ or CH₃ group within X², optionally bears on each said CH₂ or CH₃ group one or more fluoro or chloro substituents,

5 and wherein any CH₂ group which is attached to 2 carbon atoms or any CH₃ group which is attached to a carbon atom within a X² substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy and (1-3C)alkoxy;

(kkk) X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -(CR¹²R¹³)-, -(CR¹²R¹³CH₂)- and -(CH₂CR¹²R¹³)-

10 wherein each of R¹² and R¹³, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl and (1-4C)alkoxy-(1-4C)alkyl, provided that R¹² and R¹³ are not both hydrogen;

(lll) X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR^{12a})-, -(CHR^{12a}CH₂)-, -(C(R^{12a})₂CH₂)-, -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12b})-,

15 wherein each R^{12a}, which may be the same or different, is selected from (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl,

and wherein R^{12b} is selected from hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy,

(1-4C)alkylamino, di-[(1-4C)alkyl]-amino, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl,

20 amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl;

(mmm) X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR^{12a})-, -(CHR^{12a}CH₂)- and -(CH₂CHR^{12b})-

wherein R^{12a} is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl,

(1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-

25 [(1-4C)alkyl]-amino-(1-4C)alkyl,

and wherein R^{12b} is selected from hydrogen, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl,

(1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl;

(nnn) X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR^{12a})-, -(

30 (CHR^{12a}CH₂)-, -(C(R^{12a})₂CH₂)-, -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12b})-,

wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl,

and wherein R^{12b} is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-

amino;

(ooo) X^2 is selected from a group of the formula $-(CHR^{12a})-$, $-(CHR^{12a}CH_2)-$, $-(C(R^{12a})_2CH_2)-$, $-(CH_2C(R^{12a})_2)-$ and $-(CH_2CHR^{12b})-$,

wherein each R^{12a} , which may be the same or different, is (1-4C)alkyl (particularly (1-3C)alkyl),

5 and wherein R^{12b} is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-amino (particularly R^{12b} is selected from (1-4C)alkylamino and di-[(1-4C)alkyl]-amino, more particularly di-[(1-3C)alkyl]-amino);

(ppp) X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-(CHR^{12})-$, $-(CHR^{12}CH_2)-$ and $-(CH_2CHR^{12})-$,

10 wherein R^{12} is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl;

(qqq) X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-(CHR^{12a})-$, $-(CHR^{12a}CH_2)-$, $-(C(R^{12a})_2CH_2)-$, $-(CH_2C(R^{12a})_2)-$ and $-(CH_2CHR^{12a})-$,

15 wherein each R^{12a} , which may be the same or different, is (1-4C)alkyl;

(rrr) X^2 is selected from a group of the formula $-(CHR^{12a})-$, $-(CHR^{12a}CH_2)-$, $-(C(R^{12a})_2CH_2)-$, $-(CH_2C(R^{12a})_2)-$ and $-(CH_2CHR^{12a})-$ (particularly, X^2 is $-(CHR^{12a})-$), wherein each R^{12a} , which may be the same or different, is (1-4C)alkyl;

(sss) X^2 is selected from a group of the formula $-(CH_2)_q-$, wherein q is 1, 2 or 3, particularly q is 1 or 2, more particularly 1;

(ttt) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:



25 wherein X^9 is a direct bond or is selected from O, N(R^{16}), SO₂ and SO₂N(R^{16}), wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl,

(3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X^9 is a direct bond, Q^6 is heterocyclyl,

30 and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R^{17}), CO, -C=C- and -C≡C- wherein R^{17} is hydrogen or (1-6C)alkyl,

- and wherein and wherein any CH_2 or CH_3 group within any Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,
- 10 and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

$$-\text{X}^{10}-\text{R}^{18}$$

- wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $\text{N}(\text{R}^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
- 20 (uuu) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:

$$\text{Q}^6-\text{X}^9-$$

- 25 wherein X^9 is a direct bond or is selected from O, $\text{N}(\text{R}^{16})$, SO_2 and $\text{SO}_2\text{N}(\text{R}^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl, provided that when X^9 is a direct bond, Q^6 is heterocyclyl, and provided that when m, p and q are all 0, then Z is heterocyclyl, and wherein any heterocyclyl group in Z is a monocyclic fully saturated 4, 5, 6 or 7-membered heterocyclyl group containing 1 or 2 heteroatoms selected from oxygen, nitrogen and sulfur,
- 30

- and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,
- 5 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,
- 10 and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:
- $$\sim \text{X}^{10} - \text{R}^{18}$$
- wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $\text{N}(\text{R}^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl,
- 20 N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
- (vvv) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:
- $$\text{Q}^6 - \text{X}^9 -$$
- wherein X^9 is a direct bond or is selected from O and $\text{N}(\text{R}^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,
- provided that when X^9 is a direct bond, Q^6 is heterocyclyl,
- and provided that when m, p and q are all 0, then Z is heterocyclyl,
- 30 and wherein any heterocyclyl group in Z is a monocyclic non-aromatic fully saturated or partially saturated 4, 5, 6 or 7-membered monocyclic heterocyclyl group containing 1 heteroatom selected from oxygen and nitrogen and optionally a further heteroatom selected from oxygen, nitrogen and sulfur,

- and wherein and wherein any CH_2 or CH_3 group within a Z group, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,
- 10 and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:
- $$-\text{X}^{10}-\text{R}^{18}$$
- wherein X^{10} is a direct bond or is selected from O, CO, SO_2 and $\text{N}(\text{R}^{19})$, wherein R^{19} is hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
- 20 (www) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:
- $$\text{Q}^6-\text{X}^9-$$
- wherein X^9 is a direct bond or is selected from O and $\text{N}(\text{R}^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl, provided that when X^9 is a direct bond, Q^6 is heterocyclyl, and provided that when m, p and q are all 0, then Z is heterocyclyl,
- 30 and wherein any heterocyclyl group in Z is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl group may be carbon or nitrogen linked to the group to which it is attached,

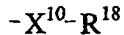
- and wherein and wherein any CH₂ or CH₃ group within a Z group, other than a CH₂ group within a heterocycl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,
- 5 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,
- 10 and wherein any heterocycl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substitutents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl,
- 15 (2-6C)alkanoyloxy and from a group of the formula:
- $$- X^{10} - R^{18}$$
- wherein X¹⁰ is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl,
- 20 N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl; (xxx) Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-(1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-
- 25 [hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl homopiperazin-1-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl and a group of the formula:
- $$Q^6-X^9-$$
- 30 wherein X⁹ is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-4C)alkyl, and Q⁶ is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocycl or heterocycl-(1-4C)alkyl,

and wherein any heterocyclyl group in Q⁶ is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, which heterocyclyl group may be carbon or nitrogen linked to the group to which it is attached,

- 5 and provided that when m, p and q are all 0, then Z is heterocyclyl, preferably one of the above mentioned heterocyclyl groups that may be represented by Q⁶, (which heterocyclyl group is preferably carbon linked to X¹),

- and wherein and wherein any CH₂ or CH₃ group within a Z group, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more
10 halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,
15 N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

- and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1,2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl,
20 (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:



- wherein X¹⁰ is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is
25 hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
(yyy) Z is selected from amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-
30 (1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino, di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, azetidin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, homopiperidin-1-yl and homopiperazin-1-yl,

and wherein and wherein any CH_2 or CH_3 group within a Z group, optionally bears on each said CH_2 or CH_3 group one or more fluoro substituents or a substituent selected from hydroxy, cyano, amino, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

- 5 and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkanoyl, (1-4C)alkylamino and di-[(1-4C)alkyl]amino,

- and provided that when m, p and q are all 0, then Z is one of the above mentioned
 10 heterocyclyl groups that may be represented by Z, such as pyrrolidin-1-yl or piperidino (preferably the sum of m +p+q is at least 1);
 (zzz) Z is selected from hydroxy, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-4C)alkoxy-(2-6C)alkoxy, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydropyranyl and a group of the formula:

- 15 $\text{Q}^6\text{-X}^9$

wherein X^9 is O, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,

- and wherein any heterocyclyl group in Q^6 is selected from tetrahydrofuranyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydropyranyl and oxepanyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl, preferably one of the above mentioned heterocyclyl groups that may be represented by Q^6 , (which heterocyclyl group is preferably carbon linked to X^1),

- and wherein any CH_2 or CH_3 group within a Z group, optionally bears on each said
 25 CH_2 or CH_3 group one or more fluoro substituents or a substituent selected from hydroxy, cyano, amino, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from
 30 halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;
 (aaaa) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy and a group of the formula:

Q^6-X^9-

wherein X^9 is a direct bond and Q^6 is heterocyclyl;

and provided that when m, p and q are all 0, then Z is heterocyclyl (preferably carbon linked to X^1),

5 and wherein any heterocyclyl group in Z is selected from azetidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl,

and wherein and wherein any CH_2 or CH_3 group within a Z group optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent

10 selected from hydroxy and (1-6C)alkoxy,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl,

15 (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (2-6C)alkanoyl,

and wherein any azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl group in Z optionally bears an oxo substituent;

(bbbb) Z is selected from hydroxy, amino, (1-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-4C)alkoxy-(2-6C)alkylamino, di-[(1-6C)alkyl]amino, N-[hydroxy-(2-6C)alkyl]-N-

20 (1-6C)alkylamino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-(1-6C)alkylamino; di-[hydroxy-(2-6C)alkyl]-amino, di-[(1-4C)alkoxy-(2-6C)alkyl]amino, N-[(1-4C)alkoxy-(2-6C)alkyl]-N-[hydroxy-(2-6C)alkyl]-amino, (1-6C)alkoxy, hydroxy-(2-6C)alkoxy and (1-4C)alkoxy-(2-6C)alkoxy,

and wherein the sum of m +p+q is at least 1;

25 (cccc) Z is selected from hydroxy, methoxy, ethoxy, 2-hydroxyethoxy, 2-methoxyethoxy, amino, methylamino, ethylamino, N-(2-hydroxyethyl)amino, N-(2-methoxyethyl)amino, dimethylamino, N-methyl-N-ethylamino, di-ethylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxyethyl)-N-ethylamino, N,N-di-(2-hydroxyethyl)amino, N-(2-methoxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-ethylamino, pyrrolidin-1-yl, piperidino, piperazin-1-yl, 30 morpholino, tetrahydrofuranyl and tetrahydropyranyl,

and wherein any heterocyclyl group within Z optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (2-4C)alkanoyl and (1-4C)alkoxy,

and provided that when m, p and q are all 0, then Z is one of the above mentioned heterocycl groups that may be represented by Z, such as tetrahydrofuranyl, pyrrolidin-1-yl or piperidino (preferably the sum of m +p+q is at least 1);

(dddd) Z is selected from pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino,

- 5 homopiperidin-1-yl, homopiperazin-1-yl, (particularly Z is selected from pyrrolidin-1-yl, piperidino, piperazin-1-yl and morpholino),

and wherein the heterocycl group within Z optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different selected from fluoro, chloro, cyano, hydroxy, amino, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino,

- 10 di-[(1-4C)alkyl]amino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, acetyl, propionyl, 2-fluoroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, hydroxyacetyl, aminoacetyl, methylaminoacetyl, ethylaminoacetyl, dimethylaminoacetyl and N-methyl-N-ethylaminoacetyl (preferably the sum of m +p+q is at least 1);

(eeee) Z is selected from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-

- 15 6C)alkoxy, hydroxy-(2-6C)alkoxy and (1-4C)alkoxy-(2-6C)alkoxy, and the sum of m +p+q is at least 1;

(ffff) Z is selected from hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-4C)alkoxy-(2-4C)alkoxy, and the sum of m +p+q is at least 1 (preferably m +p+q is 1 or 2);

(gggg) Z is hydroxy or (1-4C)alkoxy (particularly Z is hydroxy), and the sum of m +p+q is at

- 20 least 1 (preferably m +p+q is 1 or 2);

(hhhh) Z is as defined in any of (ttt) to (gggg) above,

and wherein X² is selected from -CH₂-, -CH₂CH₂-, -(CR¹²R¹³)-, -(CR¹²R¹³CH₂)-, -(CH₂CR¹²R¹³)- and (3-6C)cycloalkenylene (for example cyclopropylene such as cyclopropylidene),

- 25 wherein each of R¹² and R¹³, which may be the same or different, is selected from hydrogen, (1-4C)alkyl, hydroxy-(1-4C)alkyl, and (1-3C)alkoxy-(1-4C)alkyl, provided that R¹² and R¹³ are not both hydrogen,

and wherein X¹ is CO;

(iii) Z is as defined in any of (ttt) to (gggg) above;

- 30 X² is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR^{12a})-, -(CHR^{12a}CH₂)-, -(C(R^{12a})₂CH₂)-, -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12b})- (particularly, X² is -(CHR^{12a})-),

wherein each R^{12a}, which may be the same or different, is selected from (1-4C)alkyl, hydroxy-(1-4C)alkyl and (1-3C)alkoxy-(1-4C)alkyl,

and wherein R^{12b} is selected from hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]-amino, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, 5 amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl; and wherein X¹ is CO;

(jjjj) Z is selected from hydroxy and (1-4C)alkoxy,

X² is selected from a group of the formula -CH₂- , -CH₂CH₂- , -(CHR^{12a})- , -(CHR^{12a}CH₂)- , -(C(R^{12a})₂CH₂)- , -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12b})- (particularly, X² is 10 -(CHR^{12a})-),

wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl,

and wherein R^{12b} is selected from hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]-amino,

and wherein X¹ is CO;

15 (kkkk) Z-X²-X¹ is hydroxy-(2-4C)alkanoyl, for example hydroxyacetyl, 2-hydroxypropionyl or 3-hydroxypropionyl);

(llll) Z-X²-X¹ is (1-4C)alkoxy-(2-4C)alkanoyl, for example methoxyacetyl, 2-methoxypropionyl or 3-methoxypropionyl);

(mmmm) Z-X²-X¹ is selected from amino-(2-4C)alkanoyl, (1-4C)alkylamino-(2-4C)alkanoyl and di-[(1-4C)alkyl]amino-(2-4C)alkanoyl (for example Z-X²-X¹ is di-[(1-4C)alkyl]amino-acetyl such as dimethylaminoacetyl);

(nnnn) Z-X²- is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocyclyl is linked to the carbonyl group in Formula I, by a ring

25 carbon,

and wherein the heterocyclyl group within Z-X³ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl;

(oooo) Z-X²- is selected from tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl (for example Z-X² is selected tetrahydrofuran-2-yl or tetrahydropyran-2-yl);

(pppp) Z-X²- is selected from pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl and homopiperazinyl, which heterocycl is linked to X¹ in Formula I, by a ring carbon,

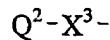
and wherein the heterocycl group within Z-X² optionally bears 1 or 2 substituents,
5 which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl; and

(qqqq) Z-X² is selected from pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperidin-1-yl and homopiperazin-1-yl,

and wherein the heterocycl group within Z-X² optionally bears 1 or 2 substituents,
10 which may be the same or different, selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl.

A particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

R¹ is selected from (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy
15 or from a group of the formula:



wherein X³ is O, and Q² is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,

and wherein any heterocycl group within a substituent on R¹ optionally bears 1, 2 or
20 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, and (2-4C)alkanoyl,

and wherein any heterocycl group within a substituent on R¹ optionally bears 1 oxo substituent;

25 b is 1, 2 or 3 (particularly b is 1 or preferably 2);

each R², which may be the same or different, is selected from fluoro, chloro, bromo and (2-4C)alkynyl;

Q¹ is selected from pyrrolidin-3-yl and azetidin-3-yl (preferably azetidin-3-yl);

a is 0 or 1 (preferably 0);

30 each W, which may be the same or different is selected from halogeno (such as fluoro), hydroxy, (1-3C)alkyl and (1-3C)alkoxy (a particular value for W is (1-3C)alkoxy);

X¹ is CO;

- X^2 is selected from a group of the formula $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CHR}^{12a})-$, $-(\text{CHR}^{12a}\text{CH}_2)-$, $-(\text{C}(\text{R}^{12a})_2\text{CH}_2)-$, $-(\text{CH}_2\text{C}(\text{R}^{12a})_2)-$ and $-(\text{CH}_2\text{CHR}^{12b})-$,
 wherein each R^{12a} , which may be the same or different, is selected from (1-4C)alkyl,
 hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-
 5 (1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl (particularly R^{12a} is (1-4C)alkyl),
 and wherein R^{12b} is selected from hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy,
 (1-4C)alkylamino, di-[(1-4C)alkyl]-amino, hydroxy-(1-4C)alkyl, (1-3C)alkoxy-(1-4C)alkyl,
 amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl and di-[(1-4C)alkyl]-amino-(1-4C)alkyl
 (particularly R^{12b} selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-amino);
 10 Z is selected from hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-4C)alkoxy-(2-4C)alkoxy, or
 $Z-X^2$ is selected from tetrahydrofuranyl, tetrahydropyrananyl, azetidinyl, pyrrolidinyl,
 piperidinyl and morpholinyl, wherein $Z-X^2$ is linked to X^1 by a ring carbon atom,
 and wherein any heterocyclyl group within Z optionally bears one or two substituents,
 15 which may be the same or different selected from fluoro, chloro, hydroxy, (1-4C)alkyl,
 (1-4C)alkoxy and (2-4C)alkanoyl,
 and wherein any azetidinyl, pyrrolidinyl or piperidinyl group in Z optionally bears an
 oxo substituent;
 provided that:
 20 when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-
 fluoroanilino and R^1 is (1-3C)alkoxy, then a is 0;
 or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.
 In this embodiment a particular value for R^1 is a group selected from (1-4C)alkoxy,
 hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy or from a group of the formula:
 25 Q^2-X^3-
 wherein X^3 is O, and Q^2 is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl,
 piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl,
 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2
 substituents, which may be the same or different, selected from halogeno, hydroxy, amino,
 30 (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino.
 In this embodiment another particular value for R^1 is a group selected from
 (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-3C)alkoxy-(2-4C)alkoxy, more particularly R^1 is

selected from (1-4C)alkoxy, such as methoxy, ethoxy, isopropoxy, particularly R¹ is methoxy).

In this embodiment a particular value for Z is a group selected from hydroxy, and (1-4C)alkoxy (for example Z is hydroxy, methoxy or ethoxy).

5 In this embodiment a particular 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino and 3-ethynylanilino. More particularly in this embodiment the 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino and 3-bromoanilino. Still more particularly the anilino
10 group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino and especially the anilino group is 3-chloro-2-fluoroanilino.

Another particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

R¹ is (1-4C)alkoxy (for example methoxy, ethoxy or isopropoxy, particularly R is
15 methoxy);

b is 1 or 2;

each R², which may be the same or different, is selected from fluoro, chloro, bromo and ethynyl;

Q¹ is azetidin-3-yl;

20 a is 0 or 1 (preferably 0);

W is (1-3C)alkyl;

X¹ is CO;

X² is selected from a group of the formula -(CHR^{12a})-, -(CHR^{12a}CH₂)-, -(CH₂CHR^{12a})-, -(C(R^{12a})₂CH₂)-, -(CH₂C(R^{12a})₂)- and -(CH₂CHR^{12b})-,
25 wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl (particularly (1-3C)alkyl),

and wherein R^{12b} is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-amino (particularly R^{12b} is selected from (1-4C)alkylamino and di-[(1-4C)alkyl]-amino, more particularly di-[(1-3C)alkyl]-amino);

30 Z is selected from hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-4C)alkoxy-(2-4C)alkoxy, or

Z-X² is selected from tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl and morpholinyl, which is linked to X¹ by a ring carbon atom,

and wherein any heterocyclyl group within Z optionally bears one or two substituents, which may be the same or different selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl;

provided that:

- 5 when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino and R¹ is (1-3C)alkoxy, then a is 0;
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.
In this embodiment a particular value for Z is a group selected from hydroxy, and (1-3C)alkoxy (for example Z is hydroxy, methoxy or ethoxy).
- 10 In this embodiment a particular 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino and 3-ethynylanilino. More particularly in this embodiment the 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino and 3-bromoanilino. Still more particularly the anilino group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino and especially the anilino group is 3-chloro-2-fluoroanilino.

Another particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

- 20 R¹ is (1-4C)alkoxy (for example methoxy, ethoxy or isopropoxy, particularly R is methoxy);

b is 1 or 2;

each R², which may be the same or different, is selected from fluoro, chloro, bromo and ethynyl;

Q¹ is azetidin-3-yl;

- 25 a is 0 or 1 (preferably 0);

W is (1-3C)alkyl;

X¹ is CO;

X² is selected from a group of the formula -(CHR^{12a})-, -(CHR^{12a}CH₂)- and -(CH₂CHR^{12a}),

- 30 wherein each R^{12a}, which may be the same or different, is (1-4C)alkyl (particularly (1-3C)alkyl);

Z is selected from hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-4C)alkoxy-(2-4C)alkoxy, or

$Z\text{-}X^2$ is selected from tetrahydrofuryl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl and morpholinyl, which is linked to X^1 by a ring carbon atom, and wherein any heterocyclyl group within Z optionally bears one or two substituents, which may be the same or different selected from fluoro, chloro, hydroxy, (1-4C)alkyl,

5 (1-4C)alkoxy and (2-4C)alkanoyl;

provided that:

when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino and R^1 is (1-3C)alkoxy, then a is 0;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

10 In this embodiment a particular value for Z is a group selected from hydroxy, and (1-3C)alkoxy (for example methoxy or ethoxy).

In this embodiment a particular 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino and 3-ethynylanilino. More particularly in this embodiment the 15 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino and 3-bromoanilino. Still more particularly the anilino group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino and especially the anilino group is 3-chloro-2-fluoroanilino.

Another particular embodiment of the present invention is a quinazoline derivative of 20 the Formula I wherein:

R^1 is (1-4C)alkoxy (for example methoxy, ethoxy, isopropoxy, particularly methoxy);

the 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino, 2-fluoro-5-chloroanilino, 3-bromoanilino and 3-

25 ethynylanilino;

Z is hydroxy or (1-4C)alkoxy, (particularly Z is hydroxy or methoxy);

Q^1 is azetidin-3-yl;

a is 0 or 1 (preferably 0);

W is (1-3C)alkyl;

30 X^1 is CO;

X^2 is selected from a group of the formula $-(\text{CHR}^{12a})-$ and $-(\text{CH}_2\text{CHR}^{12b})-$,

wherein R^{12a} is (1-4C)alkyl (particularly (1-3C)alkyl, more particularly methyl),

and wherein R^{12b} is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-amino (particularly R^{12b} is selected from (1-3C)alkylamino and di-[(1-3C)alkyl]-amino, more particularly di-[(1-3C)alkyl]-amino, still more particularly R^{12b} is methylamino and especially dimethylamino);

5 or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

In this embodiment a particular 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino and 3-bromoanilino. Still more particularly the anilino group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino and especially the anilino group is 3-chloro-2-fluoroanilino.

10 Another particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

R¹ is (1-4C)alkoxy (for example methoxy, ethoxy, isopropoxy, particularly methoxy);

the 4-anilino group in Formula I is selected from 3-chloro-4-fluoroanilino, 3-bromo-15 2-fluoroanilino, 3-chloro-2-fluoroanilino, 3-bromoanilino and 3-ethynylanilino;

Q¹ is azetidin-3-yl;

a is 0 or 1 (preferably 0);

W is (1-3C)alkyl ;

X¹ is CO;

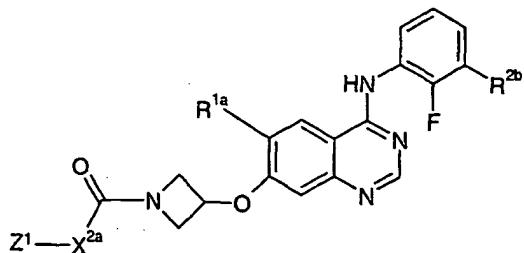
20 Z-X² is selected from tetrahydrofuryl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl and morpholinyl (particularly Z-X² is tetrahydrofuryl or pyrrolidinyl), wherein Z-X² is linked to X¹ by a ring carbon atom,

and wherein any heterocyclyl group within Z optionally bears one or two substituents, which may be the same or different selected from fluoro, chloro, hydroxy, methyl, methoxy 25 and acetyl;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

In this embodiment a particular 4-anilino group in Formula I is selected from 3-bromo-2-fluoroanilino, 3-chloro-2-fluoroanilino and 3-bromoanilino. Still more particularly the anilino group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino and especially the 30 anilino group is 3-chloro-2-fluoroanilino.

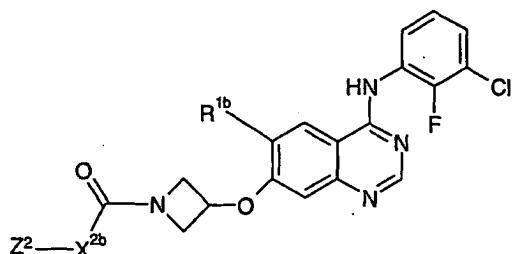
Another embodiment of the compounds of Formula I is a quinazoline derivative of the Formula Ia:



wherein:

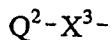
- R^{1a}** is selected from (1-3C)alkoxy, hydroxy-(2-3C)alkoxy and (1-3C)alkoxy-(2-3C)alkoxy (particularly **R^{1a}** is methoxy);
- 5 **R^{2b}** is bromo or chloro (particularly **R^{2b}** is chloro);
- X^{2a}** is selected from a group of the formula -(CHR^{12a})- and -(CH₂CHR^{12b})-,
 wherein **R^{12a}** is (1-4C)alkyl (particularly (1-3C)alkyl, more particularly methyl),
 and wherein **R^{12b}** is selected from amino, (1-4C)alkylamino and di-[(1-4C)alkyl]-
 amino (particularly **R^{12b}** is selected from (1-3C)alkylamino and di-[(1-3C)alkyl]-amino, more
10 particularly di-[(1-3C)alkyl]-amino, still more particularly **R^{12b}** is methylamino and especially
 dimethylamino);
- Z¹** is selected from hydroxy and (1-4C)alkoxy (particularly **Z¹** is hydroxy or
 methoxy),
 or the group **Z¹X^{2a}** is selected from tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl,
15 and piperidinyl, wherein **Z¹-X^{2a}** is linked to the carbonyl group by a ring carbon atom,
 and wherein any heterocyclyl group within **Z¹** optionally bears one or two
 substituents, which may be the same or different selected from fluoro, chloro, hydroxy,
 (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl,
 and when **Z¹X^{2a}** is pyrrolidinyl or piperidinyl, the pyrrolidinyl or piperidinyl group
20 optionally bears an oxo substituent;
 or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.
- In this embodiment, preferably **Z¹** is selected from hydroxy and (1-4C)alkoxy
 (particularly **Z¹** is hydroxy or methoxy and especially hydroxy).
- In this embodiment, preferably **X^{2a}** is a group of the formula -(CHR^{12a})-,
25 wherein **R^{12a}** is (1-4C)alkyl (particularly (1-3C)alkyl, more particularly methyl),

Another embodiment of the compounds of Formula I is a quinazoline derivative of the Formula Ib:

**Ib**

wherein:

- 5 R^{1b} is selected from (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy or from a group of the formula:



wherein X^3 is O, and Q^2 is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl;

- 10 X^{2b} is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR¹²)-, -(CHR¹²CH₂)- and -(CH₂CHR¹²)-

wherein R¹² is selected from (1-3C)alkyl, hydroxy-(1-3C)alkyl and (1-3C)alkoxy-(1-3C)alkyl; and

- 15 Z^2 is selected from hydroxy, (1-3C)alkoxy, hydroxy-(2-3C)alkoxy and (1-3C)alkoxy-(2-3C)alkoxy;

or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

In an embodiment in formula Ib, R^{1b} is selected from methoxy, ethoxy,

2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy (Particularly R^{1b} is (1-3C)alkoxy such as methoxy).

- 20 In another embodiment in formula Ib, X^{2b} is selected from a group of the formula -CH₂-, -CH₂CH₂- and -(CHR¹²)-, wherein R¹² is selected from (1-3C)alkyl, hydroxy-(1-3C)alkyl and (1-3C)alkoxy-(1-3C)alkyl (for example R¹² is methyl).

- 25 In another embodiment in formula Id, X^{2b} is selected from a group of the formula -CH₂- and -(CHR¹²)-, wherein R¹² is (1-3C)alkyl (for example methyl). For example X^{2b} is selected from -CH₂- and -CH(CH₃)-, particularly X^{2b} is -CH(CH₃)-.

In another embodiment in formula Id, Z^2 is selected from hydroxy and (1-3C)alkoxy, particularly Z^2 is hydroxy.

In another embodiment in formula Id, the group Z^2-X^{2b} - is selected from hydroxymethyl, methoxymethyl, (S)-1-hydroxyethyl, (R)-1-hydroxyethyl, (S)-1-methoxyethyl, (R)-1-methoxyethyl. Particularly the group Z^2-X^{2b} - is 1-hydroxyethyl, more particularly (S)-1-hydroxyethyl or (R)-1-hydroxyethyl.

- 5 In another embodiment in formula Id R^{1b} is (1-3C)alkoxy such as methoxy; and the group Z^2-X^{2b} - is selected from hydroxymethyl, methoxymethyl, (S)-1-hydroxyethyl, (R)-1-hydroxyethyl, (S)-1-methoxyethyl, (R)-1-methoxyethyl. Particularly Z^2-X^{2b} is 1-hydroxyethyl, more particularly (S)-1-hydroxyethyl or (R)-1-hydroxyethyl.

- A particular compound of the invention is, for example, a quinazoline derivative of the
- 10 Formula I selected from:
- 7-[(1-acetyl piperidin-4-yl)oxy]-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine;
N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[1-(methylsulfonyl)piperidin-4-
 yl]oxy}quinazolin-4-amine;
 (2*S*)-1-[3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidin-1-yl]-1-
- 15 oxopropan-2-ol;
 (2*R*)-1-[3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidin-1-yl]-1-oxopropan-2-ol;
N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[(3*R*)-1-(methoxyacetyl)pyrrolidin-3-
 yl]oxy}quinazolin-4-amine;
- 20 2-[(3*R*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidin-1-yl]-2-oxoethanol;
N-(3-chloro-2-fluorophenyl)-6-methoxy-7-({(3*R*)-1-[(2-methoxyethoxy)acetyl]pyrrolidin-3-
 yl}oxy)quinazolin-4-amine;
N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{[(3*R*)-1-(3-methoxypropanoyl)pyrrolidin-3-
 yl]oxy}quinazolin-4-amine;
- 25 3-[(3*R*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidin-1-yl]-3-oxopropan-1-ol; and
 5-{[4-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-
 yl]carbonyl}pyrrolidin-2-one;
- 30 or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

In a particular embodiment the invention there is provided a quinazoline derivative of the Formula I described herein, or a pharmaceutically acceptable salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt; or a pharmaceutically acceptable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes include, for example, those illustrated in WO94/27965, WO 95/03283, WO 96/33977, WO 96/33978,

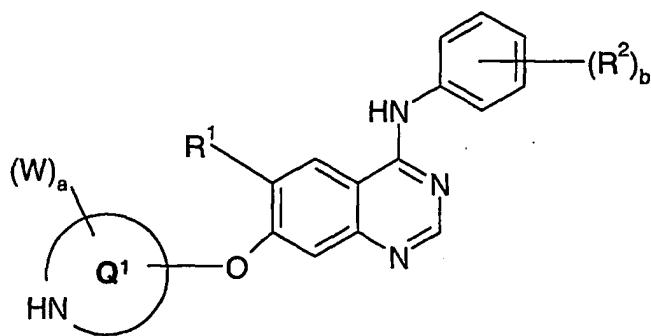
5 WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994, WO01/66099, US 5,252,586, EP 520 722, EP 566 226, EP 602 851 and EP 635 507. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1 , R^2 , X^1 , X^2 , Q^1 , W , a , b and Z have any of the meanings defined

10 hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples.

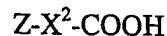
Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

15 Process (a):

For the preparation of compounds of the Formula I wherein X^1 is CO, the coupling, conveniently in the presence of a suitable base, of a quinazoline of the formula II or a salt thereof:



wherein R¹, R², W, a, b and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an acid of the formula III, or a reactive derivative thereof:



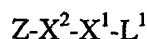
5

III

wherein Z and X² have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (b) the reaction, conveniently in the presence of a suitable base, of a quinazoline of 10 the formula II, or salt thereof, as hereinbefore defined in relation to Process (a), with a compound of the formula IV:

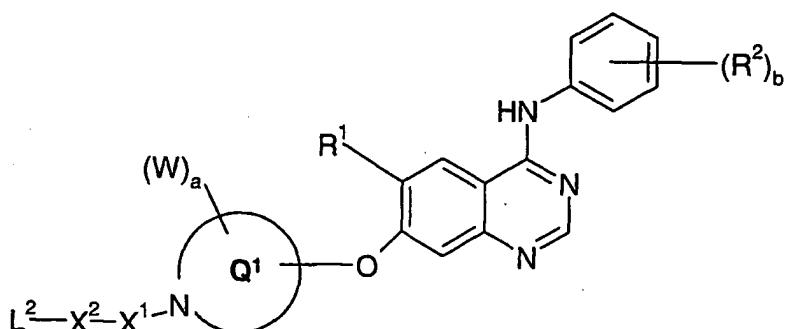
**IV**

wherein L¹ is a displaceable group and Z, X¹ and X² have any of the meanings defined

15 hereinbefore except that any functional group is protected if necessary;

or

Process (c) for the preparation of those quinazoline derivatives of the Formula I wherein Z is linked to X² by nitrogen, the reaction, conveniently in the presence of a suitable base, of a compound of the formula V:



20

V

wherein L² is a displaceable group and R¹, R², W, X¹, X², a, b and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the formula ZH, wherein Z is as hereinbefore defined, except that any

25 functional group is protected if necessary; or

Process (d)

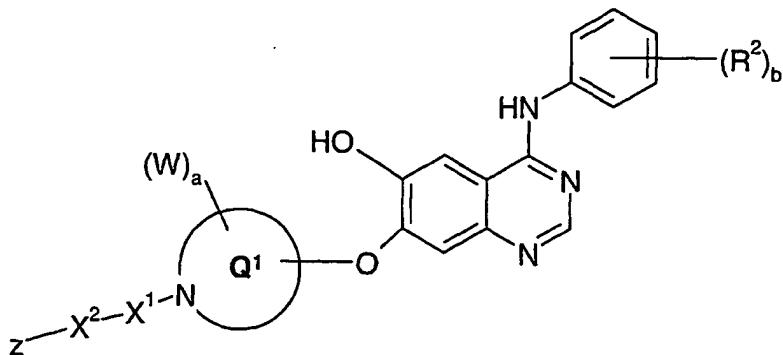
for the preparation of those quinazoline derivatives which carry a mono- or di-(1-6C)alkylamino group, the reductive amination of the corresponding quinazoline derivative of the Formula I which contains an N-H group using formaldehyde or a (2-6C) alkanolaldehyde (for example acetaldehyde or propionaldehyde); or

5 Process (e)

for the production of those quinazoline derivatives of the Formula I wherein R¹ is hydroxy, the cleavage of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy group; or

Process (f)

- 10 for the production of those quinazoline derivatives of the Formula I wherein R¹ is linked to the quinazoline ring by an oxygen atom, by coupling a compound of the Formula VI:



VI

- 15 wherein R², W, X¹, X², Z, a, b and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the formula R^{1'}OH, wherein the group R^{1'}O is one of the oxygen linked groups as hereinbefore defined for R¹ (for example (1-6C)alkoxy or Q²-O-), except that any functional group is protected if necessary;

- 20 and thereafter, if necessary (in any order):

- (i) converting a quinazoline derivative of the formula I into another quinazoline derivative of the formula I;
- (ii) removing any protecting group that is present by conventional means; and
- (iii) forming a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester.

- 25 Specific conditions for the above reactions are as follows:

Conditions for Process (a)

The coupling reaction is conveniently carried out in the presence of a suitable coupling agent, such as a carbodiimide, or a suitable peptide coupling agent, such as a uronium coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU) or O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyl uronium 5 tetrafluoroborate (TBTU); or a carbodiimide such as dicyclohexylcarbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine .

The coupling reaction is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, 10 N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate.

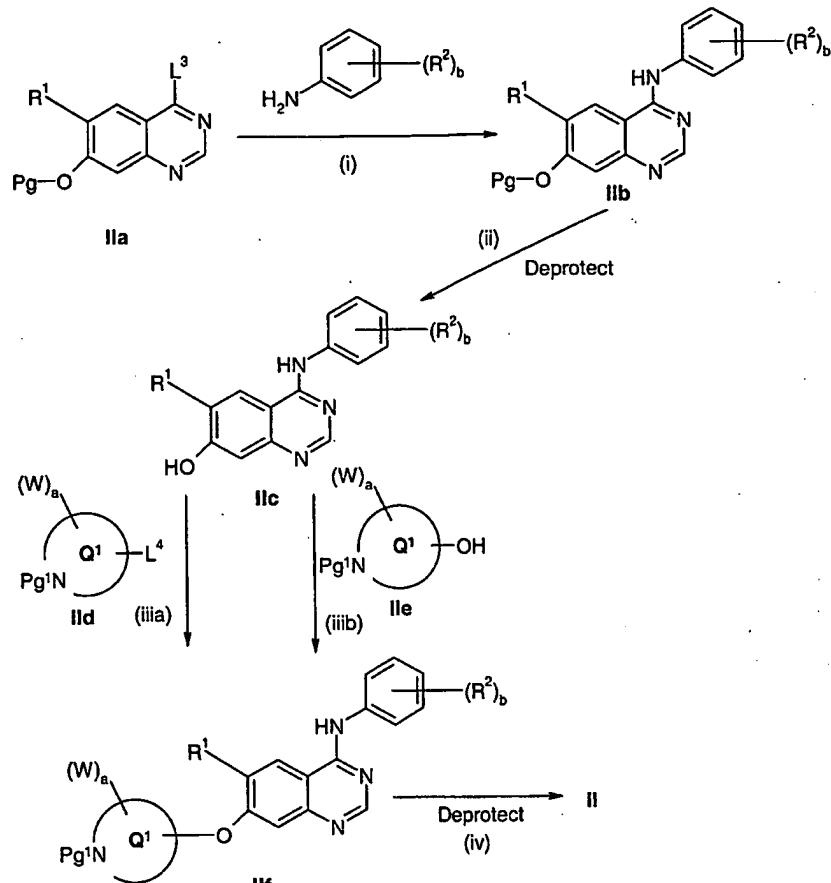
The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ester such as ethyl acetate, a halogenated solvent such as methylene 15 chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from 0 to 120°C, conveniently at or near ambient temperature.

20 By the term "reactive derivative" of the acid of the formula III is meant a carboxylic acid derivative that will react with the quinazoline of formula II to give the corresponding amide. A suitable reactive derivative of a carboxylic acid of the formula III is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an 25 anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, or N-hydroxybenzotriazole; or an acyl azide, for example an azide formed by the reaction of the acid and azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as 30 diethylphosphoryl cyanide. The reaction of such reactive derivatives of carboxylic acid with amines (such as a compound of the formula II) is well known in the art, for Example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a

temperature as described above.

Preparation of Starting Materials for Process (a)

The quinazoline of the formula II may be obtained by conventional procedures, for example as illustrated in *Reaction Scheme 1*:



5

Reaction Scheme 1

- wherein R¹, R², Q¹, W, a and b are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed
 10 by conventional means, Pg is a suitable hydroxy protecting group, Pg¹ is a suitable amino protecting group and L³ is a displaceable group.

Conditions in Reaction Scheme 1

- Step(i): Suitable hydroxy protecting groups represented by Pg are well known in the art and include those mentioned herein, for example a lower alkanoyl group such as acetyl, or a
 15 benzyl group.

A suitable displaceable group L³ is, for example, a halogeno (particularly chloro),

alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, alkylsulfonyloxy or arylsulfonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methylthio, methanesulfonyl, methanesulfonyloxy or toluene-4-sulfonyloxy group. A particular displaceable group L^3 is chloro.

5 The reaction is conveniently carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in a suitable solvent such as diethyl ether or dioxane) or hydrochloric acid.

Alternatively the quinazoline derivative of the formula **IIa**, wherein L^3 is halogeno (for example chloro), may be reacted with the aniline in the absence of an acid or a base. In 10 this reaction displacement of the halogeno leaving group L^3 results in the formation of the acid HL^3 in-situ and the autocatalysis of the reaction.

Alternatively, the reaction of the quinazoline of formula **IIa** with the aniline may be carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, 15 triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or an alkali metal hydride, for example sodium hydride, an alkali metal fluoride such as cesium fluoride, or an alkali metal disilazide such as sodium hexamethyldisilazide .

20 The above reactions are conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide,

25 N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide or acetonitrile. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently in the range 40 to 80°C or, preferably, at or near the reflux temperature of the solvent when used.

The aniline and the compound of the formula **IIa** are commercially available or can be 30 prepared using conventional methods.

Step (ii):

Deprotection using well-known methods. For example when Pg is a benzyl group it may be removed by treating the compound of formula **IIb** with a suitable acid such as

trifluoroacetic acid. Alternatively a benzyl protecting group may be removed by metal-catalysed hydrogenation, for example by hydrogenation in the presence of a palladium on carbon catalyst. Similarly, when Pg is a lower alkanoyl group such as acetyl it may be removed by hydrolysis under basic conditions, for example using ammonia, conveniently as a 5 methanolic ammonia solution.

Step (iiia):

Suitable amino protecting groups Pg₂ are well known, for example tert-butoxycarbonyl (BOC) groups.

L⁴ is a suitable displaceable group, for example as described above in relation to L², 10 such as halogeno (particularly chloro or bromo), or an alkylsulfonyloxy (particularly methanesulfonyloxy) or arylsulfonyloxy (particularly toluene-4-sulfonyloxy or 4-nitrophenylsulfonyloxy) group.

The reaction of the compound of formula IIc with the compound of formula IIId is conveniently carried out in the presence of a suitable base. Suitable bases include those 15 described above in relation to step (i), such as cesium fluoride or potassium carbonate. The reaction is conveniently carried out in the presence of a suitable inert solvent, for example, a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide or acetonitrile. The above reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently 20 in the range 40 to 80°C or, preferably, at or near the reflux temperature of the solvent when used.

Step (iiib):

An alternative to step (iiia) is the coupling of the compound of formula IIc with the alcohol of the formula IIe using the Mitsunobu coupling reaction. Suitable Mitsunobu 25 conditions are well known and include, for example, reaction in the presence of a suitable tertiary phosphine and a di-alkylazodicarboxylate in an organic solvent such as THF, or suitably dichloromethane and in the temperature range 0°C to 100°C, for example 0°C to 60°C, but suitably at or near ambient temperature. A suitable tertiary phosphine includes for example tri-n-butylphosphine or particularly tri-phenylphosphine. A suitable di-30 alkylazodicarboxylate includes, for example, diethyl azodicarboxylate (DEAD) or suitably di-tert-butyl azodicarboxylate (DTAD). Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992,

Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

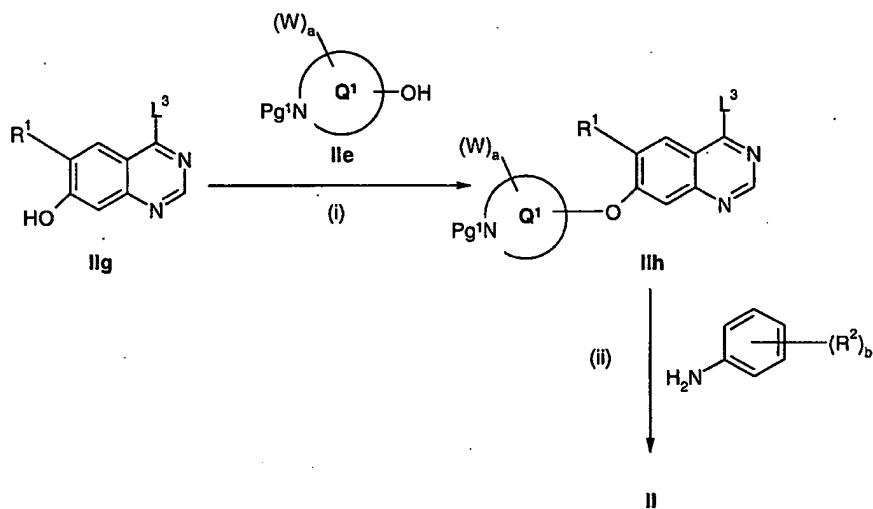
The compounds of the formulae II^d and II^e are commercially available or can be prepared using conventional methods.

5 Step (iv):

Removal of the amino protecting group Pg¹ using well known methods. For example when Pg¹ is a BOC group, by treatment with a suitable acid such as trifluoroacetic acid or hydrochloric acid.

In an alternative route to that shown in *Reaction Scheme 1*, the aniline in step (i) may 10 be reacted with the unprotected variant of the compound of the formula II^a (i.e. Pg is hydrogen), to give the compound of formula II^c directly.

The compound of formula II may also be prepared according to *Reaction Scheme 2*:



Reaction Scheme 2

15 wherein R¹, R², Q¹, W, a, b, L³ and Pg¹ are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

Conditions in Reaction Scheme 2

Step (i):

20 Coupling under Mitsunobu conditions as described above in relation to step (iiib) in *Reaction Scheme 1*.

Step (ii):

The reaction is conveniently carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in a suitable solvent such

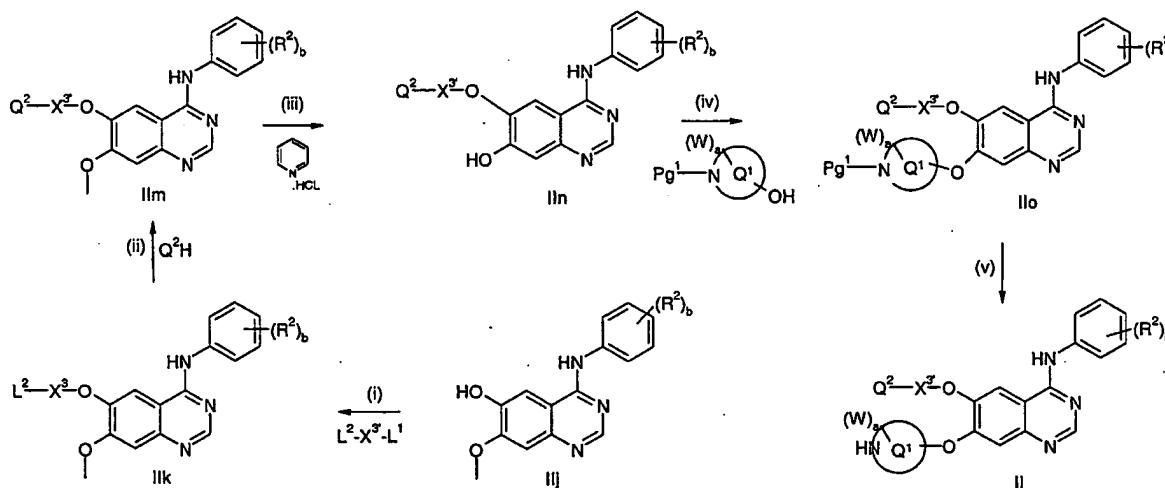
as diethyl ether or dioxane) or hydrochloric acid. The reaction is conveniently carried out in a suitable inert solvent, for example as described in step (i) of *Reaction Scheme 1*.

Conveniently, the protecting group Pg¹ is removed in-situ as a result of the acidic conditions during the aniline coupling reaction, for example when Pg¹ is tert-butoxycarbonyl.

- 5 Alternatively, the protecting group may be removed using conventional methods following the reaction.

The quinazoline of the formula IIg is commercially available or can be prepared using conventional methods.

- Quinazoline derivatives of the Formula II wherein R¹ is heterocyclyl-(2-6C)alkoxy, 10 wherein the heterocyclyl group is nitrogen linked to the (2-6C)alkoxy group may be prepared according to *Reaction Scheme 3*:



Reaction Scheme 3

- 15 wherein R¹, R², Q¹, W, X², L¹, L², a, b and Pg¹ are as hereinbefore defined, except any functional group is protected if necessary, X³ is (2-6C)-alkylene and Q² is a heterocyclyl group containing an NH ring group, and whereafter any protecting group that is present is removed by conventional means.

- Step (i): L¹ and L² are displaceable groups as defined in relation to Process (b), for example 20 halogeno such as chloro. The reaction with the compound of Formula IIj may be carried out under analogous conditions to those used in Process (b) described herein.

- The compound of Formula IIj may be prepared using standard methods, for example as described in WO03/082831 to give a compound of the Formula IIj carrying a 2,3-di-haloanilines. Analogous methods may be used to prepare compounds of the Formula IIj by 25 coupling 4-chloro-6-hydroxy-7-methoxyquinazoline with the appropriate aniline.

Step (ii): Analogous conditions to Process (b) described herein.

Step (iii): Cleavage of the methoxy group under standard conditions for such reactions, for example by treatment of the compound of Formula II^m with pyridinium hydrochloride at elevated temperature, for example from 60 to 180°C conveniently about 170°C.

- 5 Step(iv): Coupling under Mitsunobu conditions as described above in relation to step (iiib) in *Reaction Scheme 1*.

Step (v): Deprotection to remove the amine protecting group Pg¹, for example when Pg¹ is tert-butoxycarbonyl, by treating the compound of Formula (IIo) with a suitable acid such as trifluoroacetic acid.

10 Reaction Conditions for Process (b)

A suitable displaceable group L¹ includes for example halogeno such as chloro.

The reaction is conveniently performed in the presence of a suitable base, for example, conveniently in the presence of a suitable base, for example an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine,

- 15 di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, or an alkali metal hydride, for example sodium hydride, or an alkali metal disilazide such as sodium hexamethyldisilazide.

- 20 The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

- 25 The reaction is suitably carried out at a temperature of from 0°C to 30°C, conveniently at ambient temperature.

- When Z is hydroxy, the hydroxy group is conveniently protected during the reaction with the compound of Formula II. Suitable protecting groups are well known, for example an alkanoyl group such as acetyl. The protecting group may be removed following reaction with the compound of Formula II by conventional means, for example alkaline hydrolysis in the presence of a suitable base such as sodium hydroxide.

Compounds of the formula IV are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Reaction Conditions for Process (c):

A suitable displaceable group represented by L² includes, for example a halogeno or a sulfonyloxy group, for example chloro, bromo, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L² is chloro.

- The reaction is conveniently performed in the presence of a suitable base, for example
5 one of the bases described in relation to Process (b).

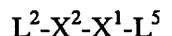
The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an ester such as ethyl acetate, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as

- 10 N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

The reaction is suitably carried out at a temperature of from 0°C to 80°C, conveniently at ambient temperature.

Preparation of Starting Materials for Process (c)

- 15 The compound of formula V used as starting material may be prepared by, for example, reacting, conveniently in the presence of a suitable base, a quinazoline of the formula II, or salt thereof, as hereinbefore defined in relation to Process (a), with a compound of the formula Va:



- 20 **Va**

wherein X¹ and X² are as hereinbefore defined, and L² and L⁵ are suitable displaceable groups, provided that L⁵ is more labile than L².

Suitable displaceable groups represented by L² and L⁵ include for example halogeno such as chloro.

- 25 The reaction is conveniently carried out in the presence of a suitable base and in a suitable inert solvent or diluent as defined above for the reaction of the quinazoline of formula V with the compound of the formula ZH.

- The compounds of the formulae ZH and Va are commercially available compounds or they are known in the literature, or they can be can be prepared by standard processes known
30 in the art.

Conveniently, in an embodiment of Process (c), a quinazoline of Formula I may be prepared directly from a quinazoline of formula II by reacting the quinazoline of formula II with a compound of formula Va and then reacting the resultant product directly with the

compound of the formula ZH without isolating the compound of formula V. This reaction enables the quinazoline of Formula I to be prepared in a single reaction vessel starting with the quinazoline of formula II.

Reaction Conditions for Process (d)

- 5 Process (d) may be used to alkylate an NH group in a quinazoline derivative of Formula I, for example when Z is amino or (1-6C)alkylamino, or when the group Z-X² carries an amino or (1-6C)alkylamino substituent. Suitable reductive amination conditions are well known in the art. For example, for the production of those quinazoline derivatives of the Formula I which contain an N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example formic acid, an alkali metal aluminium hydride such as lithium aluminium hydride, or, suitably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is suitably performed under acidic conditions in the presence of a suitable acid such as hydrogen chloride or acetic acid, a buffer may also be used to maintain pH at the desired level during the reaction. When the reducing agent is formic acid the reaction is conveniently carried out using an aqueous solution of the formic acid. The reaction is performed at a temperature in the range, for example, -10 to 100°C, such as 0 to 50°C, conveniently, at or near ambient temperature.
- 10 15 20 25 Quinazoline derivatives of the Formula I which contain an NH group (for example when Z is amino or (1-6C)alkylamino) may be prepared using one of the processes described hereinbefore. For example by coupling a compound of the Formula II with a suitable, optionally protected, amino acid using Process (a) followed by removal of any protecting groups.
- 30 Reaction conditions for Process (e)

The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. A particularly suitable cleavage reaction is the treatment of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy group with an alkali

metal halide such as lithium iodide in the presence of 2,4,6-collidine (2,4,6-trimethylpyridine). We have found that the use of 2,4,6-collidine provides selective cleavage of the (1-6C)alkoxy group at the C6 position on the quinazoline ring. The reaction may be carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore.

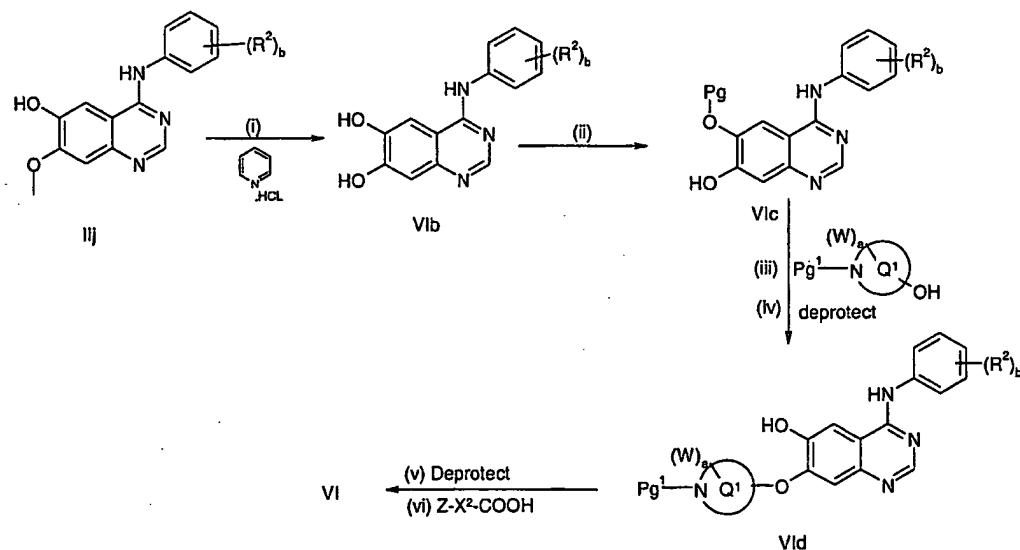
- 5 Conveniently however the reaction may be performed using only the 2,4,6-collidine without the need for additional solvents/diluents. The reaction is suitably carried out at a temperature in the range, for example, 10 to 170°C, preferably at elevated temperature for example 120 to 170°C, for example approximately 130°C.

Reaction conditions for Process (f)

- 10 The coupling reaction is conveniently carried out under Mitsunobu conditions as described above in relation to step (iiib) in *Reaction Scheme 1*.

Preparation of Starting Materials for Process (f)

- The compound of Formula VI used as starting material may be prepared by, for example, the cleavage of a quinazoline derivative of the Formula I, wherein R¹ is, for 15 example, methoxy using Process (e) described hereinbefore. Alternatively, compound of Formula VI may be prepared using conventional procedures. For example, when X¹ is CO, a compound of the Formula VI may be prepared using the method illustrated in *Reaction Scheme 4*:



20 *Reaction Scheme 4*

wherein R¹, R², Q¹, W, X², a, b, Pg and Pg¹ are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

Conditions in Reaction Scheme 4

Step (i): Cleavage of methoxy group under analogous conditions to those described in step (iii) in *Reaction Scheme 3*.

5 Step (ii) Pg is a suitable hydroxy protecting group as hereinbefore defined, for example an alkanoyl such as acetyl. The group Pg may be introduced under standard conditions for example by reacting the compound of Formula VIb with acetic anhydride.

Step (iii) Coupling under Mitsunobu conditions as described above in relation to step (iiib) in *Reaction Scheme 1*.

10 Step (iv): Deprotection to remove the protecting group Pg. For example when Pg is acetyl by alkaline hydrolysis in an alcohol, for example using a methanolic ammonia solution.

Step (v): Deprotection to remove the amine protecting group Pg¹, for example when Pg¹ is tert-butoxycarbonyl, by treating the compound of Formula (VId) with a suitable acid such a trifluoroacetic acid.

Step (vi): Coupling with acid Z-X²-COOH using the method described above for Process (a).

15 The quinazoline derivative of the Formula I may be obtained from the above processes in the form of the free base or alternatively it may be obtained in the form of a salt, an acid addition salt. When it is desired to obtain the free base from a salt of the compound of Formula I, the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium 20 carbonate, sodium hydroxide or potassium hydroxide, or by treatment with ammonia for example using a methanolic ammonia solution such as 7N ammonia in methanol.

The protecting groups used in the processes above may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods.

25 Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, 30 in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are

given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy-lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxyethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl. For example a tert butoxycarbonyl protecting group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

When a pharmaceutically acceptable ester of a quinazoline derivative of the Formula I is required, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid or alcohol using a conventional procedure as herein described in relation to definition of pharmaceutically acceptable esters.

As mentioned hereinbefore some of the compounds according to the present invention may contain one or more chiral centers and may therefore exist as stereoisomers (for example when Q¹ is pyrrolidin-3-yl). Stereoisomers may be separated using conventional techniques,

- e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash
- 5 chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. When a specific stereoisomer is isolated it is suitably isolated substantially free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other
- 10 stereoisomers.

In the section above relating to the preparation of the quinazoline derivative of Formula I, the expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

- 15 Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated
20 hereinbefore with a particular reaction).

Certain intermediates used in the processes described above are novel and form a further feature of the present invention. According to a further aspect of the present invention there is provided a quinazoline derivative of the Formula II as hereinbefore defined wherein:

- a is 2;
- 25 each R², which may be the same or different, is halogeno (particularly selected from fluoro and chloro) and wherein the R² groups are located at the ortho (2-) and meta (3-) positions on the aniline ring; and

Q¹ is a 4, 5, 6 or 7 membered saturated or partially unsaturated monocyclic heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional
30 heteroatoms selected from O, S and N, and which ring is linked to the oxygen atom in Formula I by a ring carbon, provided said heterocyclyl group is not piperidinyl; or a salt thereof. A particular compound of the Formula II is a compound of the Formula II wherein the anilino group is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino, more particularly

the anilino group is 3-chloro-2-fluoroanilino. In an embodiment in the compound of Formula II, or a salt thereof, R¹ is (1-4C)alkoxy; Q¹ is selected from azetidinyl and pyrrolidinyl and is carbon linked to the oxygen atom in formula II (preferably Q¹ is pyrrolidin-3-yl or azetidin-3-yl, more preferably Q¹ is azetidin-3-yl); a is 0 or 1; W, when present, is on a ring carbon atom 5 in Q¹ and is selected from (1-4C)alkyl, hydroxy and (1-4C)alkoxy (preferably W is 0); and the anilino group in formula II is 3-chloro-2-fluoroanilino or 3-bromo-2-fluoroanilino, more particularly the anilino group is 3-chloro-2-fluoroanilino. The intermediate of Formula II may be in the form of a salt of the intermediate. Such salts need not be a pharmaceutically acceptable salt. For example it may be useful to form prepare an intermediate in the form of a 10 pharmaceutically non-acceptable salt if, for example, such salts are useful in the manufacture of a compound of Formula I. Preferably, salts of the compound of Formula II are pharmaceutically acceptable salts as hereinbefore defined in relation to the quinazoline derivative of Formula I.

Biological Assays

15 The inhibitory activities of compounds were assessed in non-cell based protein tyrosine kinase assays as well as in cell based proliferation assays before their *in vivo* activity was assessed in Xenograft studies.

a) Protein Tyrosine Kinase phosphorylation Assays

This test measures the ability of a test compound to inhibit the phosphorylation of a 20 tyrosine containing polypeptide substrate by EGFR, erbB2 or erbB4 tyrosine kinase enzyme. Recombinant intracellular fragments of EGFR, erbB2 and erbB4 (accession numbers X00588, X03363 and L07868 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold lysis buffer (20mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 25 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM MgCl₂, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.

Constitutive kinase activity of these recombinant proteins was determined by their ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic 30 Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 200μl phosphate buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in 50mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR

or erbB2 activities were assessed by incubation in peptide coated plates for 20 minutes at room temperature in 100mM HEPES pH 7.4 at room temperature, adenosine triphosphate (ATP) at Km concentration for the respective enzyme, 10mM MnCl₂, 0.1mM Na₃VO₄, 0.2mM DL-dithiothreitol (DTT), 0.1% Triton X-100 with test compound in DMSO (final 5 concentration of 2.5%). Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.5% Tween 20).

The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature 10 with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline 15 sulfonate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate.

Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader. Kinase inhibition for a given compound was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of 20 phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b) EGFR driven KB cell proliferation assay

This assay measures the ability of a test compound to inhibit the proliferation of KB cells (human naso-pharangeal carcinoma obtained from the American Type Culture 25 Collection (ATCC)).

KB cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal calf serum, 2 mM glutamine and non-essential amino acids at 37°C in a 7.5% CO₂ air incubator. Cells were harvested from the stock flasks using Trypsin/ethylaminodiaminetetraacetic acid (EDTA). Cell density was measured using a 30 haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of 1.25x10³ cells per well of a 96 well plate in DMEM containing 2.5% charcoal stripped serum, 1mM glutamine and non-essential amino acids at 37°C in 7.5% CO₂ and allowed to settle for 4 hours.

Following adhesion to the plate, the cells are treated with or without EGF (final concentration of 1ng/ml) and with or without compound at a range of concentrations in dimethylsulfoxide (DMSO) (0.1% final) before incubation for 4 days. Following the incubation period, cell numbers were determined by addition of 50 μ l of 3-(4,5-

- 5 Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then tipped off, the plate gently tapped dry and the cells dissolved upon the addition of 100 μ l of DMSO.

Absorbance of the solubilised cells was read at 540nm using a Molecular Devices ThermoMax microplate reader. Inhibition of proliferation was expressed as an IC₅₀ value.
10 This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus EGF) and negative (vehicle minus EGF) control values.

c) **Clone 24 phospho-erbB2 cell assay**

This immunofluorescence end point assay measures the ability of a test compound to
15 inhibit the phosphorylation of erbB2 in a MCF7 (breast carcinoma) derived cell line which was generated by transfecting MCF7 cells with the full length erbB2 gene using standard methods to give a cell line that overexpresses full length wild type erbB2 protein (hereinafter 'Clone 24' cells).)

Clone 24 cells were cultured in Growth Medium (phenol red free Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal bovine serum, 2 mM glutamine and 1.2mg/ml G418) in a 7.5% CO₂ air incubator at 37°C. Cells were harvested from T75 stock flasks by washing once in PBS (phosphate buffered saline, pH7.4, Gibco No. 10010-015) and harvested using 2mls of Trypsin (1.25mg/ml) / ethylaminodiacetate acid (EDTA) (0.8mg/ml) solution. The cells were resuspended in Growth Medium. Cell density
25 was measured using a haemocytometer and viability was calculated using Trypan Blue solution before being further diluted in Growth Medium and seeded at a density of 1x10⁴ cells per well (in 100 μ l) into clear bottomed 96 well plates (Packard, No. 6005182).

3 days later, Growth Medium was removed from the wells and replaced with 100 μ l Assay Medium (phenol red free DMEM, 2mM glutamine, 1.2mg/ml G418) either with or
30 without erbB inhibitor compound. Plates were returned to the incubator for 4hrs and then 20 μ l of 20% formaldehyde solution in PBS was added to each well and the plate was left at room temperature for 30 minutes. This fixative solution was removed with a multichannel pipette,

100µl of PBS was added to each well and then removed with a multichannel pipette and then 50µl PBS was added to each well. Plates were then sealed and stored for up to 2 weeks at 4°C.

- Immunostaining was performed at room temperature. Wells were washed once with 200µl PBS / Tween 20 (made by adding 1 sachet of PBS / Tween dry powder (Sigma, No. P3563) to 1L of double distilled H₂O) using a plate washer then 200µl Blocking Solution (5% Marvel dried skimmed milk (Nestle) in PBS /Tween 20) was added and incubated for 10 minutes. Blocking Solution was removed using a plate washer and 200µl of 0.5% Triton X-100 / PBS was added to permeabilise the cells. After 10 minutes, the plate was washed with 200µl PBS / Tween 20 and then 200µl Blocking Solution was added once again and incubated for 15 minutes. Following removal of the Blocking Solution with a plate washer, 30µl of rabbit polyclonal anti-phospho ErbB2 IgG antibody (epitope phospho-Tyr 1248, SantaCruz, No. SC-12352-R), diluted 1:250 in Blocking Solution, was added to each well and incubated for 2 hours. Then this primary antibody solution was removed from the wells using a plate washer followed by two 200µl PBS / Tween 20 washes using a plate washer. Then 30µl of Alexa-Fluor 488 goat anti-rabbit IgG secondary antibody (Molecular Probes, No. A-11008), diluted 1:750 in Blocking Solution, was added to each well. From now onwards, wherever possible, plates were protected from light exposure, at this stage by sealing with black backing tape. The plates were incubated for 45 minutes and then the secondary antibody solution was removed from the wells followed by two 200ul PBS / Tween 20 washes using a plate washer. Then 100µl PBS was added to each plate, incubated for 10 minutes and then removed using a plate washer. Then a further 100µl PBS was added to each plate and then, without prolonged incubation, removed using a plate washer. Then 50µl of PBS was added to each well and plates were resealed with black backing tape and stored for up to 2 days at 4°C before analysis.
- The Fluorescence signal in each well was measured using an Acumen Explorer Instrument (Acumen Bioscience Ltd.), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning. The instrument was set to measure the number of fluorescent objects above a pre-set threshold value and this provided a measure of the phosphorylation status of erbB2 protein. Fluorescence dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Inhibition of erbB2 phosphorylation was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of erbB2 phosphorylation signal.

d) In vivo Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a LoVo tumour (colorectal adenocarcinoma obtained from the ATCC) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype).

- 5 Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. LoVo tumour cell (colorectal adenocarcinoma obtained from the ATCC) xenografts were established in the hind flank of
10 donor mice by sub cutaneous injections of 1×10^7 freshly cultured cells in 100 μ l of serum free media per animal. On day 5 post-implant, mice were randomised into groups of 7 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/10g body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula (length x width) x $\sqrt{(length \times width)} \times (\pi/6)$, where length
15 was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of study was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

Although the pharmacological properties of the compounds of the Formula I vary with
20 structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

- Test (a):- IC₅₀ in the range, for example, 0.001 - 1 μ M;
Test (b):- IC₅₀ in the range, for example, 0.001 - 5 μ M;
25 Test (c):- IC₅₀ in the range, for example, 0.01 - 5 μ M;
Test (d):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as
30 defined hereinbefore is administered at the dosage ranges defined hereinafter.

By way of example, using Test (a) (for the inhibition of EGFR tyrosine kinase protein phosphorylation) and Test (b), the KB cell assay described above, representative compounds described in the Examples herein gave the IC₅₀ results shown below in Table A:

Table A

Compound of Example	IC ₅₀ (nM) Test (a) (Inhibition of EGFR tyrosine kinase protein phosphorylation)	IC ₅₀ (nM) Test (b) (EGFR driven KB cell proliferation assay)
3	17	71
4	8	48
5	217	119
6[5]	41	397

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an

appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a quinazoline derivative of the formula I will naturally vary according to the nature and severity of the 5 conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a quinazoline derivative of the formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general 10 lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain 15 about 0.5 mg to 0.5 g of a compound of this invention.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB family receptor tyrosine kinase inhibitory activity, particularly inhibition of the EGF receptor (erbB1) tyrosine kinase. Furthermore, certain of the compounds according to the present 20 invention possess substantially better potency against the EGF receptor tyrosine kinase, than against other tyrosine kinase enzymes, for example erbB2. Such compounds possess sufficient potency against the EGF receptor tyrosine kinase that they may be used in an amount sufficient to inhibit EGF receptor tyrosine kinase whilst demonstrating little, or significantly lower, activity against other tyrosine kinase enzymes such as erbB2. Such 25 compounds are likely to be useful for the selective inhibition of EGF receptor tyrosine kinase and are likely to be useful for the effective treatment of, for example EGF driven tumours.

Accordingly, the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB receptor tyrosine kinases (especially EGF receptor tyrosine kinase), i.e. the compounds may be used to 30 produce an erbB receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by inhibition of one or more of the erbB family of receptor tyrosine kinases. Particularly the compounds of the invention may be used to

- produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone or in part by the inhibition of erbB receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of one or more of the erbB receptor tyrosine kinases, such as
- 5 EGF and/or erbB2 and/or erbB4 receptor tyrosine kinases (especially EGF receptor tyrosine kinase) that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment of psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and/or cancer by providing an anti-proliferative effect,
- 10 particularly in the treatment of erbB receptor tyrosine kinase sensitive cancers. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung (especially non-small-cell lung), neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin,
- 15 testicular, thyroid, uterine and vulval cancers.

According to this aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use as a medicament.

- According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use in the production of an anti-proliferative effect in a warm-blooded animal such as a human.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as a human.

- According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as a human, 30 in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to

5 inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR) tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours in a warm-blooded animal such as a

10 human which are sensitive to inhibition of one or more of the erbB family of receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR) tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a

15 pharmaceutically acceptable ester thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use in the prevention or treatment of those tumours in a warm-blooded animal such as a human which are sensitive to inhibition of erbB receptor tyrosine

20 kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR) tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore in the manufacture of a

25 medicament for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect in a warm-blooded animal such as a human.

According to a further feature of this aspect of the invention there is provided a method for providing a EGFR and/or an erbB2 and or an erbB4 (especially a EGFR) tyrosine kinase inhibitory effect in a warm-blooded animal such as a human which comprises

30 administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect in a warm-blooded animal such as a human.

- 5 According to a further feature of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human.
- 10 According to a further feature of this aspect of the invention there is provided a method for providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore.
- 15 According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use in providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human.

By "a selective EGFR kinase inhibitory effect" is meant that the quinazoline derivative of Formula I is more potent against EGF receptor tyrosine kinase than it is against other kinases. In particular some of the compounds according to the invention are more potent against EGF receptor kinase than it is against other tyrosine kinases such as other erbB receptor tyrosine kinases such erbB2. For example a selective EGFR kinase inhibitor according to the invention is at least 5 times, preferably at least 10 times more potent against EGF receptor tyrosine kinase than it is against erbB2 tyrosine kinase, as determined from the relative IC₅₀ values in suitable assays. For example, by comparing the IC₅₀ value from the KB cell assay (a measure of the EGFR tyrosine kinase inhibitory activity) with the IC₅₀ value from the Clone 24 phospho-erbB2 cell assay (a measure of erb-B2 tyrosine kinase inhibitory activity) for a given test compound as described above.

20 According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer (for example a cancer selected from

leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung (especially non-small-cell lung), neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer) in a warm-blooded animal such as a human..

- 5 According to a further feature of this aspect of the invention there is provided a method for treating a cancer (for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung (especially non-small-cell lung), neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer) in a
10 warm-blooded animal, such as a human, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt, or a pharmaceutically acceptable ester thereof, as defined hereinbefore.

- According to a further aspect of the invention there is provided a compound of the
15 Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, for use in the treatment of a cancer (for example selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung (especially non-small-cell lung), neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer) in a
20 warm-blooded animal such as a human.

- As mentioned above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease will necessarily be varied depending upon, amongst other things, the host treated, the route of administration and the severity of the illness being treated.

- 25 The anti-proliferative treatment/tyrosine kinase inhibitory effect defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-
(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical
30 oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example

- anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and
- 5 teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and
- 10 buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);
- 15 (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, MEK inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example other inhibitors of the epidermal growth factor family (for example
- 20 other EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example
- 25 inhibitors of the hepatocyte growth factor family;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and
- 30 compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiotatin);

- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;
- (vii) antisense therapies, for example those which are directed to the targets listed above, such
- 5 as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or
- 10 radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as
- 15 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.
- (x) Cell cycle inhibitors including for example CDK inhibitors (eg flavopiridol) and other inhibitors of cell cycle checkpoints (eg checkpoint kinase); inhibitors of aurora kinase and other kinases involved in mitosis and cytokinesis regulation (eg mitotic kinesins); and histone
- 20 deacetylase inhibitors

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

- 25 According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the Formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

- Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required
- 30 to inhibit the effects of the erbB receptor tyrosine protein kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

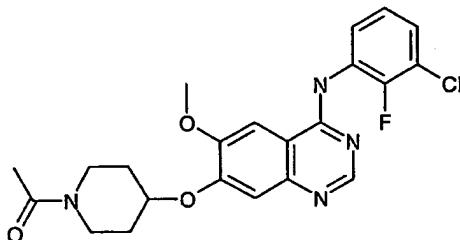
- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;
- 5 (ii) organic solutions were dried over anhydrous magnesium sulfate or sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- 10 (iv) in general, the course of reactions was followed by TLC and / or analytical LCMS, and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- (vi) yields are given for illustration only and are not necessarily those which can be obtained
- 15 by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at the operating frequency of the NMR apparatus used (300 or 400 MHz), using perdeuterio dimethyl sulfoxide (DMSO-d₆) as solvent unless otherwise indicated; the
- 20 following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- (ix) solvent ratios are given in volume:volume (v/v) terms;
- (x) mass spectra (MS) were run using a Waters or Micromass electrospray LC-MS in positive
- 25 or negative ion mode; values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is (MH)⁺;
- (xi) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;
- (xii) melting points (mp) were measured using a Buchi B-545 Automated melting point
- 30 apparatus;
- (xiii) unless stated otherwise compounds containing an asymmetrically substituted carbon atom were not resolved; and
- (xiv) the following abbreviations have been used:

HATU O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-Tetramethyluronium Hexafluoro-
Phosphate;

	DIPEA:	diisopropylethylamine;
	DMA:	N,N-dimethylacetamide;
5	DMF:	N,N-dimethylformamide;
	DCM	dichloromethane;
	DMSO:	dimethylsulfoxide
	EtOAc:	ethyl acetate;
	IPA:	isopropyl alcohol;
10	TFA:	trifluoroacetic acid; and
	THF:	tetrahydrofuran.

Example 1

7-[(1-Acetyl piperidin-4-yl)oxy]-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-
15 amine



Acetyl chloride (64 mg) in methylene chloride (5ml) was added to a solution of N-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (250 mg) and diisopropylethylamine (300 µl) in methylene chloride (20 ml) dropwise, such
20 that the temperature of the mixture remained < 5°C. The reaction mixture was allowed to warm to room temperature and stand overnight. This was then washed with saturated aqueous sodium bicarbonate (50 ml), dried over MgSO₄, filtered and evaporated to a white foam. The resulting product was then purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/methanol (100/0 to 95/5). The fractions containing the
25 desired product were combined and evaporated under vacuum to give the title product as a colourless foam (181 mg); ¹H NMR Spectrum: (DMSO-d₆) 1.50 -1.65 (m, 1H), 1.65-1.80 (m, 1H), 1.91-2.15 (m, 2H), 2.04 (s, 3H), 3.20-3.33 (m, 1H), 3.33-3.47 (m, 1H), 3.65-3.80 (m, 1H), 3.85-4.02 (m, 1H), 3.95 (s, 3H), 4.90 (m, 1H), 7.30 (m, 1H), 7.35 (s, 1H), 7.40-7.60 (m, 2H), 7.82 (s, 1H), 8.39 (s, 1H), 9.60 (s, 1H); Mass Spectrum: (M+H)⁺ 445.

The *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride used as starting material was prepared as follows:

4.0M HCl in Dioxane (4.0 ml) was added to a stirred suspension of 7-(benzyloxy)-4-chloro-6-methoxyquinazoline (prepared as described in WO98/13354, Example 1) (60 g, 0.2 mol) and 3-chloro-2-fluoroaniline (31.96 g, 0.22 mol) in acetonitrile (1200 ml). The reaction mixture was heated at 80°C for 1 hour then left to stand overnight. Acetonitrile (500 ml) was added and the resulting precipitate filtered, washed with acetonitrile (3 x 500 ml) and dried under vacuum to give 7-(benzyloxy)-*N*-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride as a beige solid (85.45 g, 96%); 1H NMR Spectrum: (DMSO d₆) 4.02 (s, 3H), 5.35 (s, 2H), 7.30-7.60 (m, 9H), 7.65 (m, 1H), 8.38 (s, 1H), 8.85 (s, 1H), 11.8 (s, 1H); Mass Spectrum: (M+H)⁺ 410.

A solution of 7-(benzyloxy)-*N*-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride (85.45g, 0.192mol) in trifluoroacetic acid (300 ml) was heated at 80°C for 1 hour. The reaction mixture was the evaporated to dryness and the residues re-dissolved 15 in methanol (200ml). This solution was then added dropwise to a stirred aqueous solution of saturated sodium bicarbonate (500ml). The resulting precipitate was collected by filtration, washed with acetonitrile and dried under vacuum. The resulting solids were then purified by hot (100°C) trituration with a mixture of butanone (500 ml) and MeOH (100ml), filtered and dried to 4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-ol as a cream solid (45 g, 73%); 20 1H NMR Spectrum: (DMSO d₆): 3.98 (s, 3H), 7.10 (s, 1H), 7.25-7.30 (m, 1H), 7.40-7.50 (m, 1H), 7.50-7.60 (m, 1H), 7.80 (s, 1H), 8.30 (s, 1H), 9.55 (s, 1H), 10.32 (s, 1H); Mass Spectrum: (M+H)⁺ 320.

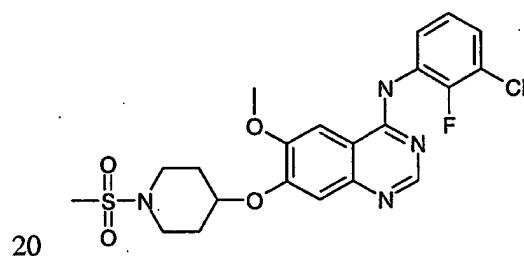
4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-ol (500 mg, 1.565 mmol) was dissolved in DMA (20 ml). *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate 25 (436.6 mg, 1.565 mmol) and cesium fluoride (236.3 mg, 1.565 mmol) were added, and the mixture was heated to 60°C with stirring. After 18 hours, *tert*-butyl 4-methanesulfonyloxy piperidine-1-carboxylate and cesium fluoride were again added in the same quantities to the reaction mixture and heating was continued at 60°C for a further 18 hours. The solvent was evaporated, and the residue was partitioned between saturated 30 aqueous sodium bicarbonate solution (50ml) and EtOAc (2x50ml). The organics were combined, dried over MgSO₄ and evaporated. The resulting product was then purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/EtOAc (100/0 to 0/100). The fractions containing the desired product were combined

and evaporated under vacuum to give *tert*-butyl 4-(*{*4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidine-1-carboxylate as a colourless foam (757 mg, 96%);
¹H NMR Spectrum: (DMSO-d₆): 1.52 (s, 9H), 1.60-1.80 (m, 2H), 2.02-2.20 (m, 2H), 3.20-3.45 (m, 2H), 3.75-3.92 (m, 2H), 4.05 (s, 3H), 4.95 (m, 1H), 7.32-7.45 (m, 2H), 7.55-7.70 (m, 2H), 7.92 (s, 1H), 8.50 (s, 1H), 9.73 (s, 1H); Mass Spectrum: (M+H)⁺ 503.

Trifluoroacetic acid (50 ml) was added to a solution of *tert*-butyl 4-(*{*4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidine-1-carboxylate (750 mg, 1.49 mmol) in methylene chloride (1 ml) and triethylsilane (1 ml) and the solution stirred for 1 hour. The reaction mixture was then evaporated under reduced pressure and the residues re-dissolved in EtOAc (5 ml). This solution was then treated with 1M HCl/diethylether (1 ml) followed by more diethylether (50 ml) to give a white precipitate. The resulting solids were collected following centrifugation and dried under vacuum to give *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride as a white solid (750 mg);
¹H NMR Spectrum: (DMSO-d₆): 2.00-2.20 (m, 2H), 2.25-2.45 (m, 2H), 3.15-3.50 (m, 4H), 4.15 (s, 3H), 5.02 (m, 1H), 7.48 (m, 1H), 7.60-7.85 m, 3H), 8.35 (s, 1H), 8.85 (s, 1H), 9.56 (bs, 2H); Mass Spectrum : (M+H)⁺ 403.

Example 2

N-(3-Chloro-2-fluorophenyl)-6-methoxy-7-{[1-(methylsulfonyl)piperidin-4-yl]oxy}quinazolin-4-amine

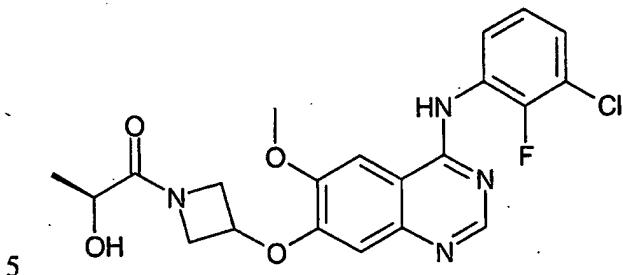


Using an analogous procedure to that described in Example 1, methanesulphonyl chloride (43 µl) reacted with *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine dihydrochloride (220 mg, 0.50 mmol). The resulting product was then purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/methanol (100/0 to 97/3). The fractions containing the desired product were combined and evaporated under vacuum to give the title product as a colourless foam (145.6 mg, 60.5%); ¹H NMR Spectrum: (DMSO-d₆): 1.70-1.90 (m, 2H), 2.04-2.20 (m, 2H), 2.92 (s, 3H), 3.10-3.25 (m, 2H), 3.35-3.45 (m, 2H), 3.95 (s, 3H), 4.83 (m, 1H), 7.30 (m, 1H), 7.34 (s, 1H), 7.40-7.60 (m, 2H), 7.83 (s, 1H), 8.40 (s, 1H), 9.65 (s, 1H); Mass Spectrum: (M+H)⁺ 481.

Example 3

(2S)-1-[3-({4-[3-Chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidin-1-yl]-1-oxopropan-2-ol

(Process (a))



HATU (0.102g) was added to a stirred solution of 7-(azetidin-3-yloxy)-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride (100 mg), N-methylmorpholine (0.15 ml) and L-lactic acid (0.024 g) in DMF (10 ml) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was evaporated to dryness and the residues 10 were partitioned between ethyl acetate (20 ml) and water (10 ml). The organics were then purified by flash column chromatography on SiO₂ eluting with increasingly polar mixtures of methanol and methylene chloride (0/100 – 10/ 90). Appropriate fractions were combined and evaporated to give a foam. This was triturated with diethyl ether / iso-hexane (1:1) to give the title product as a white solid (0.073 g); ¹H NMR Spectrum: (DMSO d₆) 1.20 (d, 3H), 3.80-15 3.95 (m, 1H), 3.97 (s, 3H), 4.15 (q, 1H), 4.27 (m, 1H), 4.41 (m, 1H), 4.80 (m, 1H), 5.12 (m, 1H), 5.25 (m, 1H), 6.95 (s, 1H), 7.27 (dd, 1H), 7.40-7.57 (m, 2H), 7.83 (s, 1H), 8.39 (s, 1H), 9.67 (s, 1H); Mass Spectrum: (M+H)⁺ 447.

The 7-(azetidin-3-yloxy)-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride starting material was prepared as follows:

20 A solution of 4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-ol (1.23 g, 3.85 mmol, prepared as described in Example 1, preparation of starting materials), triphenylphosphine (1.51 g, 5.78 mmol) and 3-hydroxy-azetidine-1-carboxylic acid tert-butyl ester (1.0 g, 5.78 mmol, commercially available, or may be prepared using known methods, for example by hydrogenation of 1-(diphenylmethyl)azetidin-3-ol (Synlett 1991, (11) 783-25 784)) in methylene chloride (25 ml) was cooled to 0°C under a nitrogen atmosphere. A solution of di-*tert*-butyl azodicarboxylate (1.33 g, 5.78 mmol) in methylene chloride (5 ml) was then added dropwise and the reaction mixture was allowed to warm to room temperature and stir for 18 hours. The mixture was then filtered and the filtrates were purified by column chromatography eluting with increasingly polar mixtures of methylene chloride/EtOAc (100/0

to 0/100). The fractions containing the desired product were combined and evaporated under vacuum to give *tert*-butyl 3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidine-1-carboxylate as a colourless foam (620 mg); Mass Spectrum: (M+H)⁺ 475.

- 4M HCl in dioxane (20 ml) was added to a stirred solution of *tert*-butyl 3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidine-1-carboxylate (620 mg, 1.30 mmol) in acetonitrile (20 ml) and the mixture heated to 60°C. After 1 hour the resulting precipitate was collected by filtration, washed with diethylether (20 ml) and dried under vacuum to give 7-(azetidin-3-yloxy)-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride as a white solid (334 mg); ¹H NMR Spectrum: (DMSO-d₆): 4.05 (s, 3H), 4.0-4.25 (m, 2H), 4.4-4.55 (m, 2H), 5.3 (m, 1H), 7.3-7.42 (m, 2H), 7.52 (dd, 1H), 7.62 (dd, 1H), 8.55 (s, 1H), 8.83 (s, 1H), 9.4-9.7 (m, 2H), 12.05 (s, 1H); Mass Spectrum: (M+H)⁺ 375.

Example 4

(2*R*)-1-[3-({4-[3-Chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)azetidin-1-yl]-1-oxopropan-2-ol

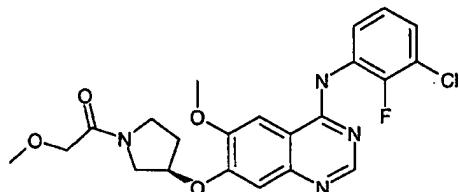
- 15 (Process (a))

D-lactic acid was coupled with 7-(azetidin-3-yloxy)-N-(3-chloro-2-fluorophenyl)-6-methoxyquinazolin-4-amine hydrochloride using an analogous method to that described in Example 3 to give the title product; ¹H NMR Spectrum: (DMSO d₆) 1.20 (d, 3H), 3.80-3.95 (m, 1H), 3.97 (s, 3H), 4.15 (q, 1H), 4.27 (m, 1H), 4.41 (m, 1H), 4.80 (m, 1H), 5.12 (m, 1H), 5.25 (m, 1H), 6.95 (s, 1H), 7.27 (dd, 1H), 7.40-7.57 (m, 2H), 7.83 (s, 1H), 8.39 (s, 1H), 9.67 (s, 1H); Mass Spectrum: (M+H)⁺ 447.

Example 5

N-(3-Chloro-2-fluorophenyl)-6-methoxy-7-[(3*R*)-1-(methoxyacetyl)pyrrolidin-3-yl]oxy]quinazolin-4-amine

- 25 (Process (a))



HATU (0.31 g) was added to a solution of N-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*R*)-pyrrolidin-3-yloxy]quinazolin-4-amine dihydrochloride (300 mg), diisopropylethylamine (0.45 ml) and methoxyacetic acid (0.086 g) in methylene chloride (10

ml) and the mixture was stirred at room temperature for 2.5 hours. Methylene chloride (20 ml) was added and the organic layer was washed with aqueous sodium hydroxide (2M, 30 ml) and water (30 ml). The resulting product was purified by flash column chromatography eluting with methanol (4%) and methylene chloride (96%) to give a foam. This was re-

- 5 precipitated by stirring in diethyl ether (20 ml) to give the title product as a white solid (0.142 g); ¹H NMR Spectrum: (DMSO d₆) 2.18 (m, 1H), 2.32 (m, 1H), 3.30 (s, 3H)*, 3.33 (s, 3H)*, 3.38-3.56 (m, 1H), 3.60-3.88 (m, 3H), 3.97 (s, 3H), 4.04 (s, 2H)*, 4.09 (s, 2H)*, 5.28 (m, 1H)*, 5.38 (m, 1H)*, 7.28 (m, 2H), 7.52 (m, 2H), 7.82 (s, 1H), 8.40 (s, 1H), 9.65 (br s, 1H); Mass Spectrum : (M+H)⁺ 461; melting point 73 to 77°C.

10 * rotameric signals

The *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*R*)-pyrrolidin-3-yloxy]quinazolin-4-amine dihydrochloride used as starting material was prepared as follows:

- Di-*tert*-butylazodicarboxylate (5.41 g) was added dropwise to a mixture of *tert*-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (4.39 g), 4-[3-chloro-2-fluoroanilino]-6-15 methoxyquinazolin-7-ol (5.00 g, prepared as described in Example 1, preparation of starting materials) and triphenylphosphine (6.16 g) in methylene chloride (115 ml). The solution was stirred at room temperature for 1.5 hours. The mixture was purified by flash column chromatography eluting with isohexane/acetone/triethylamine (82/17/1) to give *tert*-butyl (3*R*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidine-1-20 carboxylate as a yellow foam (11.40 g) containing some triphenylphosphine oxide which was used directly; Mass Spectrum: (M+H)⁺ 489.

4.0M HCl in dioxane (7.0 ml) was added to a stirred suspension of *tert*-butyl (3*R*)-3-((4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidine-1-carboxylate (11.40 g) in acetonitrile (50 ml). The reaction mixture was heated at 70°C and left at this 25 temperature overnight. Filtration of the white solid gave *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*S*)-pyrrolidin-3-yloxy]quinazolin-4-amine dihydrochloride as a solid (5.66 g); ¹H NMR Spectrum: (DMSO d₆) 2.28 (m, 1H), 2.40 (m, 1H), 3.25-3.75 (m, 4H), 4.04 (s, 3H), 5.35 (m, 1H), 7.35 (m, 1H), 7.53 (m, 1H), 7.61 (m, 2H), 8.59 (s, 1H), 8.84 (s, 1H), 9.60(br s, 1H), 9.90 (br s, 1H); Mass Spectrum: (M+H)⁺ 389.

30 Example 6

Using a similar procedure to that described in Example 5, *N*-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*R*)-pyrrolidin-3-yloxy]quinazolin-4-amine dihydrochloride was coupled with the appropriate carboxylic acid to give the compounds shown in Table 1:

Table 1

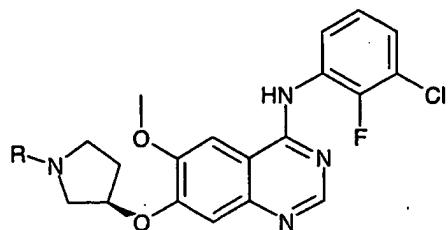
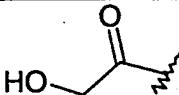
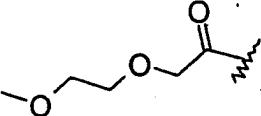
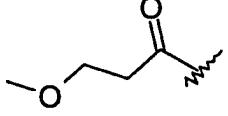
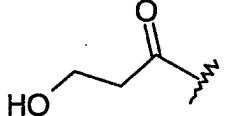
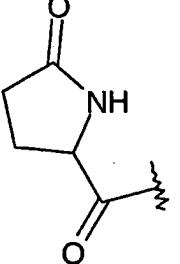


Table 1

No. and Note	R
[1]	
[2]	
[3]	
[4]	
[5]	

5 Notes:

In Table 1 ^{wavy line} refers to the point of attachment of the carbonyl group in Table 1 to the nitrogen in the pyrrolidin-3-yl group.

In the following notes, a * in an NMR spectrum refers to rotameric signals.

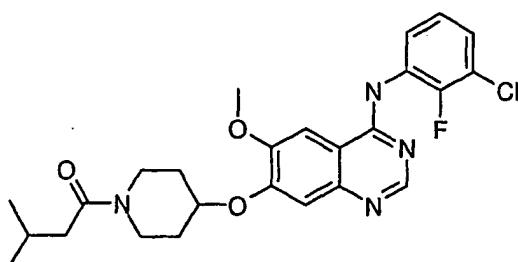
- [1] **2-[(3*R*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidin-1-yl]-2-oxoethanol.** Following the coupling reaction, the product was purified as described in Example 5 to give the title product as a white solid; ¹H NMR Spectrum: (DMSO d₆) 2.18 (m, 1H), 2.29 (m, 1H), 3.37-3.84 (m, 4H), 3.94 (s, 3H), 3.98-4.10 (m, 2H), 4.60 (m, 1H), 5.27 (m, 1H)*, 5.37 (m, 1H)*, 7.29 (m, 2H), 7.52 (m, 2H), 7.83 (s, 1H), 8.40 (s, 1H), 9.67 (br s, 1H); Mass Spectrum: (M+H)⁺ 447; melting point 210 to 213°C.
- [2] **N-(3-chloro-2-fluorophenyl)-6-methoxy-7-((3*R*)-1-[(2-methoxyethoxy)acetyl]pyrrolidin-3-yl}oxy)quinazolin-4-amine.** Following the coupling reaction, the product was purified as described in Example 5 to give the title product as a white solid (0.128 g); ¹H NMR Spectrum: (DMSO d₆) 2.16 (m, 1H), 2.29 (m, 1H), 3.22 (s, 3H)*, 3.29 (s, 3H)*, 3.38-3.90 (m, 8H), 3.96 (s, 3H), 4.09 (s, 2H)*, 4.13 (s, 2H)*, 5.27 (m, 1H)*, 5.36 (m, 1H)*, 7.28 (m, 2H), 7.52 (m, 2H), 7.82 (s, 1H), 8.40 (s, 1H), 9.64 (br s, 1H); Mass Spectrum: (M+H)⁺ 505; melting point 75 to 79°C.
- [3] **N-(3-chloro-2-fluorophenyl)-6-methoxy-7-[(3*R*)-1-(3-methoxyprop酰)pyrrolidin-3-yl]oxy}quinazolin-4-amine.** Following the coupling reaction, the product was purified as described in Example 5 to give the title product as a white solid; (0.099 g); ¹H NMR Spectrum: (DMSO d₆) 2.25 (m, 2H), 2.54 (m, 2H), 3.21 (s, 3H)*, 3.27 (s, 3H)*, 3.40 (m, 1H), 3.52-3.90 (m, 5H), 3.96 (s, 3H), 5.27 (m, 1H)*, 5.33 (m, 1H)*, 7.28 (m, 2H), 7.52 (m, 2H), 7.83 (s, 1H), 8.40 (s, 1H), 9.63 (br s, 1H); Mass Spectrum: (M+H)⁺ 475; melting point 199 to 202°C.
- [4] **3-[(3*R*)-3-({4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)pyrrolidin-1-yl]-3-oxopropan-1-ol.** Following the coupling reaction, the product was purified by flash column chromatography eluting with methanol (5%) and methylene chloride (95%) to give a foam. This was re-precipitated by stirring in diethyl ether (20 ml) to give the title product as a white solid (0.056 g); ¹H NMR Spectrum: (DMSO d₆) 2.25 (m, 2H), 2.57 (m, 2H), 3.39 (m, 1H), 3.53-3.77 (m, 5H), 3.95 (s, 3H), 4.50 (m, 1H), 5.28 (m, 1H)*, 5.33 (m, 1H)*, 7.28 (m, 2H), 7.52 (m, 2H), 7.84 (s, 1H), 8.40 (s, 1H), 9.69 (br s, 1H); Mass Spectrum: (M+H)⁺ 461; melting point 100 to 102°C.
- [5] **5-[(4-[3-chloro-2-fluoroanilino]-6-methoxyquinazolin-7-yl}oxy)piperidin-1-yl]carbonyl}pyrrolidin-2-one;** ¹H NMR Spectrum: ((DMSO + CD₃COOD): 1.64-1.89 (m, 2H); 1.89-1.99 (m, 1H); 2.04 -2.23 (m, 4H); 2.31-2.43 (m, 1H); 3.32-3.54 (m, 2H); 3.73-3.86 (m, 1H); 3.89-3.98 (m, 1H); 4.03 (s, 3H); 4.94 (bs, 1H); 7.62 (dd, 1H); 7.41 (ddd, 1H); 7.50

(s, 1H); 7.58 (ddd, 1H); 7.68 (ddd, 1H); 8.12 (s, 1H); 8.92 (s, 1H); Mass Spectrum: (M+H)⁺ 514.

Example 7

**N-(3-chloro-2-fluorophenyl)-6-methoxy-7-{{[1-(3-methylbutanoyl)piperidin-4-
5 yl]oxy}quinazolin-4-amine**

(process (b))



N-(3-Chloro-2-fluorophenyl)-6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-amine

10 (500 mg, 1.05 mmol) and 4-dimethylaminopyridine (128 mg, 1.05 mmol) were stirred in acetonitrile (2.5 ml) and diisopropylethylamine (0.366 ml, 2.10 mmol) was added. The mixture was cooled to 0°C and a solution of isovaleryl chloride (0.160 ml, 1.31 mmol) in acetonitrile (0.5 ml) was added drop-wise. The reaction mixture was then stirred at this temperature for 0.5 hours. Water (1.0 ml) and potassium hydroxide (0.641 ml of a 49% w/w
15 solution in water) were added. The layers were partitioned and the organic layer diluted with ethyl acetate (2.5 ml). Water was added followed by glacial acetic acid (0.210 ml). The mixture was stirred and partitioned. The organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the title product (416mg, 81%) as a white solid; ¹H NMR Spectrum: (DMSO_d₆) 0.92 (d, 6H); 1.61 (m, 2H); 2.01 (m, 3H); 2.23
20 (dd, 2H); 3.24 (m, 1H); 3.40 (m, 1H); 3.78 (m, 1H); 3.95 (m, 4H); 4.90 (m, 1H); 7.29 (dt, 1H); 7.35 (s, 1H); 7.51 (m, 2H); 7.83 (s, 1H); 8.39 (s, 1H); 9.63 (s, 1H); Mass Spectrum: (M+H)⁺ 487.

Example 8

Pharmaceutical compositions

25 The following illustrates representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X") which may be prepared, for therapeutic or prophylactic use in humans:

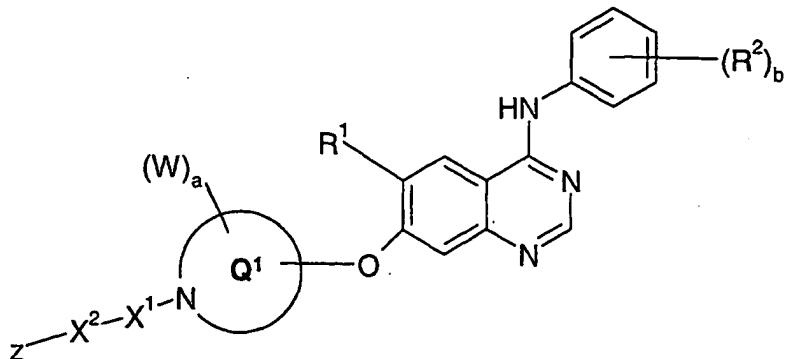
	(a) Tablet I	mg/tablet
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
5	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
	(b) Injection I	(50 mg/ml)
10	Compound X.....	5.0% w/v
	1M Sodium hydroxide solution.....	15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)	
	Polyethylene glycol 400.....	4.5% w/v
	Water for injection to 100%.	

15

The above compositions may be prepared by conventional procedures well known in the pharmaceutical art. For example, Tablet I may be prepared by blending the components together and compressing the mixture into a tablet.

CLAIMS

- ## 1. A quinazoline derivative of the Formula I:



5

II

wherein:

R¹ is selected from hydrogen, hydroxy, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

10 Q²-X³-

wherein X³ is a direct bond or is O, and Q² is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹

15 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R³), CO, CH(OR³), CON(R³), N(R³)CO, SO₂N(R³), N(R³)SO₂, CH=CH and C≡C wherein R³ is hydrogen or (1-6C)alkyl.

and wherein any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl,

20 (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

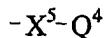
O³-X⁴-

wherein X⁴ is a direct bond or is selected from CO and N(R⁴)CO, wherein R⁴ is hydrogen or

25 (1-6C)alkyl, and Q³ is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent, other than a CH_2 group within a heterocyclyl ring, optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio,

- 5 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and
- 10 N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:

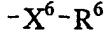


wherein X^5 is a direct bond or is selected from O, S, SO , SO_2 , $\text{N}(\text{R}^5)$, CO, $\text{CH}(\text{OR}^5)$, $\text{CON}(\text{R}^5)$, $\text{N}(\text{R}^5)\text{CO}$, $\text{SO}_2\text{N}(\text{R}^5)$, $\text{N}(\text{R}^5)\text{SO}_2$, $\text{C}(\text{R}^5)_2\text{O}$, $\text{C}(\text{R}^5)_2\text{S}$ and $\text{C}(\text{R}^5)_2\text{N}(\text{R}^5)$, wherein R^5 is hydrogen or (1-6C)alkyl, and Q^4 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-

- 15 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears one or more (for example 1, 2 or 3) substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl,

- 20 mercapto, sulfamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
- 25 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:



wherein X^6 is a direct bond or is selected from O, $\text{N}(\text{R}^7)$ and $\text{C}(\text{O})$, wherein R^7 is hydrogen or

- 30 (1-6C)alkyl, and R^6 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl,
N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or
(1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
5 oxo or thioxo substituents;

b is 1, 2, 3, 4 or 5;

each R², which may be the same or different, is selected from halogeno, cyano, nitro,
hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl,
(2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio,
10 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
(1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-
6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,
15 N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulphonylamino, N-(1-
6C)alkyl-(1-6C)alkanesulphonylamino and a group of the formula:

15 -X⁷-R⁸

wherein X⁷ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-
6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-
6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-
20 6C)alkoxycarbonylamino-(1-6C)alkyl;

Q¹ is a 4, 5, 6 or 7 membered saturated or partially unsaturated monocyclic
heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional
heteroatoms selected from O, S and N, and which ring is linked to the oxygen atom in
Formula I by a ring carbon;

25 a is 0, 1, 2, 3 or 4;

each W, which may be the same or different, is selected from halogeno,
trifluoromethyl, cyano, nitro, hydroxy, oxo, amino, formyl, mercapto, (1-6C)alkyl,
(1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino,
di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, (2-6C)alkanoyloxy and from a group of the formula:

30 -X⁸-R¹⁰

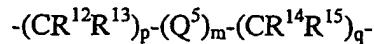
wherein X⁸ is a direct bond or is selected from O, CO, SO₂ and N(R¹¹), wherein R¹¹ is
hydrogen or (1-6C)alkyl, and R¹⁰ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,
N-(1-6C)alkylamino-(1-6C)alkyl or N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl;

X^1 is selected from CO and SO₂;

X^2 is a group of the formula:

5



wherein m is 0 or 1, p is 0, 1, 2, 3 or 4 and q is 0, 1, 2, 3 or 4,

each of R¹², R¹³, R¹⁴ and R¹⁵, which may be the same or different, is selected from hydrogen, (1-6C)alkyl, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and Q⁵ is selected from (3-7C)cycloalkylene and (3-7C)cycloalkenylene,

10

and wherein any CH₂ or CH₃ group within an X² group, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

Z is selected from hydrogen, hydroxy, amino, (1-6C)alkylamino,

di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino,

15

N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:



wherein X⁹ is a direct bond or is selected from O, N(R¹⁶), SO₂ and SO₂N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and Q⁶ is (3-7C)cycloalkyl,

(3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-4C)alkyl,

20 heterocyclyl or heterocyclyl-(1-4C)alkyl,

provided that when X⁹ is a direct bond, Q⁶ is heterocyclyl,

and provided that when m, p and q are all 0, then Z is heterocyclyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO,

25 SO₂, N(R¹⁷), CO, -C=C- and -C≡C- wherein R¹⁷ is hydrogen or (1-6C)alkyl,

and wherein and wherein any CH₂ or CH₃ group within any Z group, other than a CH₂ group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,

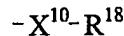
30 (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,

(2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,

N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,

and wherein any heterocyclyl group within a Z substituent optionally bears one or more (for example 1, 2 or 3) substituents which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C) alkanoyl, (2-6C) alkanoyloxy and from a group of the formula:



10 wherein X^{10} is a direct bond or is selected from O, CO, SO₂ and N(R¹⁹), wherein R¹⁹ is hydrogen or (1-4C)alkyl, and R¹⁸ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl,

and wherein any heterocyclyl group within a Z substituent optionally bears 1 or 2 oxo substituents, provided that said oxo substituent(s) is not on a ring carbon which is adjacent to a ring oxygen in the heterocyclyl group;

15 provided that:

(i) when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-2-fluoroanilino, R¹ is hydrogen or (1-3C)alkoxy, and X¹ is CO, then a is 0 and Z is selected 20 from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q⁶-X⁹-; and

(ii) when Q¹ is piperidinyl, Z is hydrogen;
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

25

2. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

R¹, R², W, X¹, X², a and b are as defined in claim 1; and

Z is selected from hydrogen, hydroxy, amino, (1-6C)alkylamino,

30 di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino and a group of the formula:



- wherein X^9 is a direct bond or is selected from O, N(R^{16}), SO₂ and SO₂N(R^{16}), wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-4C)alkyl, (3-7C)cycloalkenyl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl,
- 5 provided that when X^9 is a direct bond, Q^6 is heterocyclyl,
and provided that when m, p and q are all 0, then Z is heterocyclyl,
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a Z substituent
are optionally separated by the insertion into the chain of a group selected from O, S, SO,
SO₂, N(R^{17}), CO, -C=C- and -C≡C- wherein R^{17} is hydrogen or (1-6C)alkyl,
- 10 and wherein and wherein any CH₂ or CH₃ group within any Z group, other than a CH₂
group within a heterocyclyl ring, optionally bears on each said CH₂ or CH₃ group one or more
halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino,
carboxy, carbamoyl, sulfamoyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,
(1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
- 15 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,
(2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,
N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulfonylamino,
and wherein any heterocyclyl group within a Z substituent optionally bears one or
20 more (for example 1, 2 or 3) substituents which may be the same or different, selected from
halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, formyl, mercapto, (1-6C)alkyl,
(2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl,
(1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl,
(2-6C)alkanoyloxy and from a group of the formula:
- 25 $-X^{10}-R^{18}$
- wherein X^{10} is a direct bond or is selected from O, CO, SO₂ and N(R^{19}), wherein R^{19} is
hydrogen or (1-4C)alkyl, and R^{18} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl,
(1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl,
N-(1-4C)alkylamino-(1-4C)alkyl and N,N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
- 30 provided that:
(i) when the 4-anilino group in Formula I is 4-bromo-2-fluoroanilino or 4-chloro-
2-fluoroanilino, R^1 is hydrogen or (1-3C)alkoxy, and X^1 is CO, then a is 0 and Z is selected
from hydroxy, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxy, (1-

6C)alkylsulfonyl, (1-6C)alkanesulfonylamino, N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, and a group of the formula Q⁶-X⁹-; and

(ii) when Q¹ is piperidinyl, Z is hydrogen.

5 3. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 or claim 2 wherein:

R¹ is selected from hydrogen, (1-6C)alkoxy, cyclopropyl-(1-4C)alkoxy, cyclobutyl-(1-4C)alkoxy, cyclopentyl-(1-4C)alkoxy, cyclohexyl-(1-6C)alkoxy, tetrahydrofuranyl-(1-4C)alkoxy and tetrahydropyranyl-(1-4C)alkoxy,

10 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of an O atom,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more fluoro or chloro substituents, or a substituent selected from hydroxy and (1-3C)alkoxy.

15

4. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein R¹ is (1-3C)alkoxy.

20 5. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

b is 1, 2 or 3; and
each R², which may be the same or different, is selected from fluoro, chloro, bromo, and
25 (2-4C)alkynyl.

6. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

30 b is 1 or 2 and one R² is at the meta (3-) position on the anilino group in Formula 1 and is chloro or bromo.

7. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of claims 1 to 4 wherein the anilino group at the 4-position on the quinazoline ring in Formula I is selected from 3-chloro-2-bromoanilino, 3-chloro-2-fluoroanilino, 3-ethynylanilino and 3-bromoanilino.

5

8. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims wherein:

X^2 is selected from a group of the formula $-CH_2-$, $-CH_2CH_2-$, $-(CHR^{12a})-$, $-10 (CHR^{12a}CH_2)-$, $-(C(R^{12a})_2CH_2)-$, $-(CH_2C(R^{12a})_2)-$ and $-(CH_2CHR^{12a})-$,
wherein each R^{12a} , which may be the same or different, is (1-4C)alkyl.

9. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims
15 wherein:

Q^1 is azetidin-3-yl;

a is 0 or 1; and

W is (1-3C)alkyl.

20 10. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims
wherein:

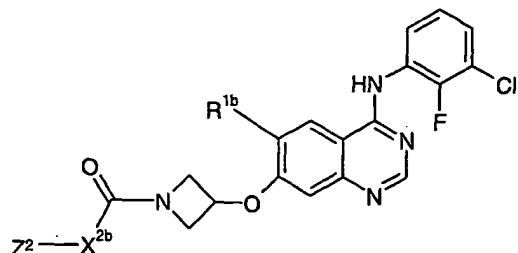
Z is selected from hydroxy, (1-4C)alkoxy, hydroxy-(2-4C)alkoxy and (1-4C)alkoxy-(2-4C)alkoxy), and the sum of $m+p+q$ is at least 1.

25

11. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims
wherein X^1 is CO.

30 12. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of the preceding claims
wherein the group $Z-X^2-X^1$ is selected from hydroxy-(2-4C)alkanoyl and (1-4C)alkoxy-(2-4C)alkanoyl.

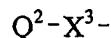
13. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 of the Formula Ib:



Ib

5 wherein:

R^{1b} is selected from (1-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-3C)alkoxy-(2-4C)alkoxy or from a group of the formula:



wherein X³ is O, and Q² is azetidin-1-yl-(2-4C)alkyl, pyrrolidin-1-yl-(2-4C)alkyl, 10 piperidino-(2-4C)alkyl, piperazino-(2-4C)alkyl or morpholino-(2-4C)alkyl;

X^{2b} is selected from a group of the formula -CH₂-, -CH₂CH₂-, -(CHR¹²)-, -(CHR¹²CH₂)- and -(CH₂CHR¹²)-

wherein R¹² is selected from (1-3C)alkyl, hydroxy-(1-3C)alkyl and (1-3C)alkoxy-(1-3C)alkyl; and

15 **Z²** is selected from hydroxy, (1-3C)alkoxy, hydroxy-(2-3C)alkoxy and (1-3C)alkoxy-(2-3C)alkoxy.

14. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to claim 1 wherein:

20 **R¹** is (1-4C)alkoxy;

b is 1 or 2;

each **R²**, which may be the same or different, is selected from fluoro, chloro, bromo and ethynyl;

Q¹ is azetidin-3-yl;

25 **a** is 0;

W is (1-3C)alkyl;

X¹ is CO;

X^2 is selected from a group of the formula $-(\text{CHR}^{12a})-$, $-(\text{CHR}^{12a}\text{CH}_2)-$ and $-(\text{CH}_2\text{CHR}^{12a})-$,

wherein R^{12a} is (1-4C)alkyl;

Z is selected from hydroxy and (1-4C)alkoxy, or

- 5 $Z\text{-}X^2$ is selected from tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl and morpholinyl, which is linked to X^1 by a ring carbon atom,
and wherein any heterocyclyl group within Z optionally bears one or two substituents, which may be the same or different selected from fluoro, chloro, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkanoyl.

10

15. A quinazoline derivative of the Formula I according to claim 1 selected from:
 $7-[(1\text{-acetyl} \text{piperidin}-4\text{-yl})\text{oxy}]\text{-}N\text{-}(3\text{-chloro-2-fluorophenyl})\text{-}6\text{-methoxy} \text{quinazolin-4-amine};$
 $N\text{-}(3\text{-chloro-2-fluorophenyl})\text{-}6\text{-methoxy-7-}\{[1\text{-}(methylsulfonyl)\text{piperidin-4-yl}]\text{oxy}\}\text{quinazolin-4-amine};$
- 15 $(2S)\text{-}1\text{-}[3\text{-}\{4\text{-}[3\text{-chloro-2-fluoroanilino]-6-methoxy} \text{quinazolin-7-yl}\}\text{oxy}]\text{azetidin-1-yl}\text{-}1\text{-oxopropan-2-ol};$
 $(2R)\text{-}1\text{-}[3\text{-}\{4\text{-}[3\text{-chloro-2-fluoroanilino]-6-methoxy} \text{quinazolin-7-yl}\}\text{oxy}]\text{azetidin-1-yl}\text{-}1\text{-oxopropan-2-ol};$
 $N\text{-}(3\text{-chloro-2-fluorophenyl})\text{-}6\text{-methoxy-7-}\{[(3R)\text{-}1\text{-}(methoxyacetyl)\text{pyrrolidin-3-yl}]\text{oxy}\}\text{quinazolin-4-amine};$
- 20 $2\text{-}\{[3R)\text{-}3\text{-}\{4\text{-}[3\text{-chloro-2-fluoroanilino]-6-methoxy} \text{quinazolin-7-yl}\}\text{oxy}\}\text{pyrrolidin-1-yl}\text{-}2\text{-oxoethanol};$
 $N\text{-}(3\text{-chloro-2-fluorophenyl})\text{-}6\text{-methoxy-7-}\{[(3R)\text{-}1\text{-}\{[2\text{-methoxyethoxy}]\text{acetyl}\}\text{pyrrolidin-3-yl}]\text{oxy}\}\text{quinazolin-4-amine};$
- 25 $N\text{-}(3\text{-chloro-2-fluorophenyl})\text{-}6\text{-methoxy-7-}\{[(3R)\text{-}1\text{-}(3\text{-methoxypropanoyl})\text{pyrrolidin-3-yl}]\text{oxy}\}\text{quinazolin-4-amine};$
 $3\text{-}\{[3R)\text{-}3\text{-}\{4\text{-}[3\text{-chloro-2-fluoroanilino]-6-methoxy} \text{quinazolin-7-yl}\}\text{oxy}\}\text{pyrrolidin-1-yl}\text{-}3\text{-oxopropan-1-ol};$ and
 $5\text{-}\{[4\text{-}\{4\text{-}[3\text{-chloro-2-fluoroanilino]-6-methoxy} \text{quinazolin-7-yl}\}\text{oxy}\}\text{piperidin-1-yl}\text{carbonyl}\}\text{pyrrolidin-2-one};$
or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

16. A quinazoline derivative of the Formula I according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof.
17. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt or, a pharmaceutically acceptable ester thereof, according to any one of the preceding claims, in association with a pharmaceutically-acceptable diluent or carrier.
18. A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, according to any one of claims 1 to 16, for use as a medicament.
19. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as a human.
20. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16 in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of EGFR tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation of tumour cells.
21. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16 in the manufacture of a medicament for use in providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human.
22. Use of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16 in the manufacture of a medicament for use in the treatment of a cancer in a warm-blooded animal such as a human.

23. A method for producing an anti-proliferative effect in a warm-blooded animal, such as a human, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16.

5

24. A method for the prevention or treatment of those tumours in a warm-blooded animal such as a human which are sensitive to inhibition of EGFR tyrosine kinases, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative 10 of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16.

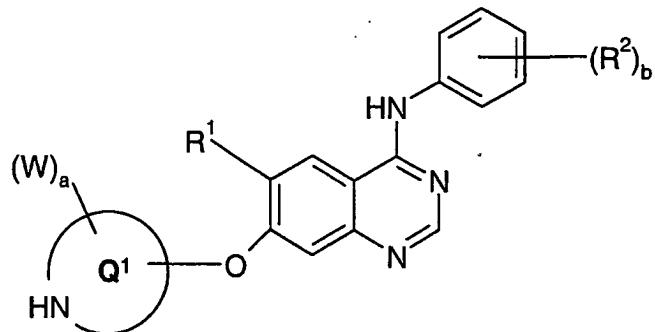
25. A method for providing a selective EGFR tyrosine kinase inhibitory effect in a warm-blooded animal such as a human which comprises administering to said animal an effective 15 amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16.

26. A method for treating a cancer in a warm-blooded animal, such as a human, in need of such treatment, which comprises administering to said animal an effective amount of a 20 quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof, as defined in any one of claims 1 to 16.

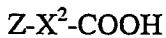
27. A process for the preparation of a quinazoline derivative of the Formula I as defined in Claim 1 which comprises:

25 Process (a):

for the preparation of compounds of the Formula I wherein X¹ is CO, the coupling of a quinazoline of the formula II or a salt thereof:

**II**

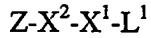
wherein R¹, R², W, a, b and Q¹ are as defined in claim 1, except that any functional group is protected if necessary, with an acid of the formula **III**, or a reactive derivative thereof:

**III**

wherein Z, X¹ and X² are as defined in claim 1, except that any functional group is protected if necessary;

10 or

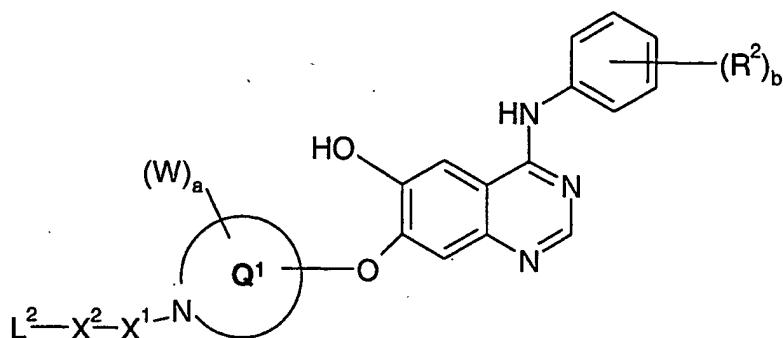
Process (b) the reaction of a quinazoline of the formula **II** or a salt thereof, as defined in relation to Process (a), with a compound of the formula **IV**:

**IV**

15 wherein L¹ is a displaceable group and Z, X¹ and X² are as defined in claim 1, except that any functional group is protected if necessary;

or

Process (c) for the preparation of those quinazoline derivatives of the Formula I wherein Z is linked to X² by nitrogen, the reaction of a compound of the formula **V**:



V

wherein L^2 is a displaceable group and R^1 , R^2 , W , X^1 , X^2 , a , b and Q^1 are as defined in
5 claim 1, except that any functional group is protected if necessary, with a compound of the formula ZH , wherein Z is as hereinbefore defined, except that any functional group is
protected if necessary; or

Process (d)

for the preparation of those quinazoline derivatives which carry a mono- or di-(1-
10 6C)alkylamino group, the reductive amination of the corresponding quinazoline derivative of
the Formula I which contains an N-H group using formaldehyde or a (2-6C)alkanolaldehyde;
or

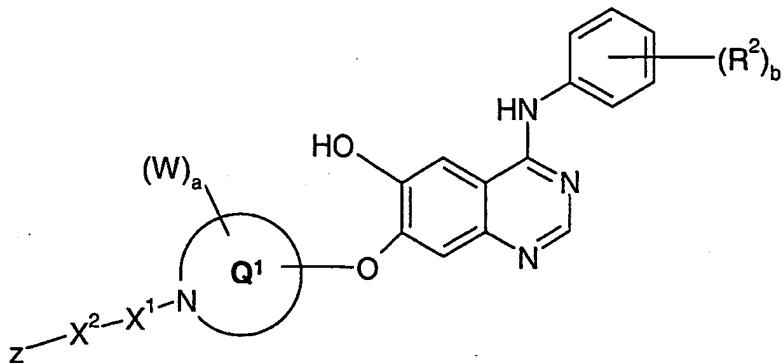
Process (e)

for the production of those quinazoline derivatives of the Formula I wherein R^1 is
15 hydroxy, the cleavage of a quinazoline derivative of the Formula I wherein R^1 is a (1-
6C)alkoxy group; or

Process (f)

for the production of those quinazoline derivatives of the Formula I wherein R^1 is
linked to the quinazoline ring by an oxygen atom, by coupling a compound of the Formula

20 VI:



VI

wherein R², W, X¹, X², Z, a, b and Q¹ are as defined in claim 1, except that any functional group is protected if necessary, with a compound of the formula R'¹OH, wherein
5 the group R'¹O is one of the oxygen linked groups as defined for R¹ in claim 1, except that any functional group is protected if necessary;

and thereafter, if necessary (in any order):

- (i) converting a quinazoline derivative of the Formula I into another quinazoline derivative of the Formula I;
- 10 (ii) removing any protecting group that is present by conventional means; and
- (iii) forming a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester of the quinazoline derivative of the Formula I.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/003915

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12 C07D401/12 C07D401/14 A61K31/517 A61P35/00
 //((C07D403/12, 239:00, 211:00), (C07D401/12, 239:00, 205:00), (C07D401/12
 239:00, 207:00), (C07D401/14, 239:00, 207:00, 207:00))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2004/006846 A (KENNEDY ABIGAIL R ; KIM ANGIE I (US); BUSSENIUS JOERG (US); COSTANZA S) 22 January 2004 (2004-01-22) claim 1	1-27
X	WO 00/55141 A (METZ THOMAS ; SOLCA FLAVIO (AT); BOEHRINGER INGELHEIM PHARMA (DE); HIM) 21 September 2000 (2000-09-21) cited in the application claim 1	1-27
X	WO 98/13354 A (LOHMANN JEAN JACQUES MARCEL ; HENNEQUIN LAURENT FRANCOIS AND (FR); ZEN) 2 April 1998 (1998-04-02) cited in the application claim 1	1-27
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

2 December 2004

Date of mailing of the International search report

10/12/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2340, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3C15

Authorized officer

Wörth, C

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB2004/003915

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/51991 A (METZ THOMAS ; SOLCA FLAVIO (AT); BOEHRINGER INGELHEIM PHARMA (DE); HIM) 8 September 2000 (2000-09-08) claim 1	1-27
A	WO 97/30035 A (ZENECA LTD ; ZENECA PHARMA SA (FR); THOMAS ANDREW PETER (GB); JOHNSTON) 21 August 1997 (1997-08-21) claim 1	1-27
A	HENNEQUIN L F ET AL: "Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 5369-5389, XP002164236 ISSN: 0022-2623 table 2	1-27
A	HENNEQUIN L F ET AL: "Novel 4-anilinoquinazolines with C-7 basic side chains: Design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, no. 6, 14 March 2002 (2002-03-14), pages 1300-1312, XP002256124 ISSN: 0022-2623 table 4	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/003915

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple Inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB2004/003915

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2004006846	A	22-01-2004	WO	2004006846 A2		22-01-2004
WO 0055141	A	21-09-2000	DE	19911509 A1		21-09-2000
			AU	772520 B2		29-04-2004
			AU	3166700 A		04-10-2000
			BG	105893 A		31-05-2002
			BR	0009076 A		26-12-2001
			CA	2368059 A1		21-09-2000
			CN	1343201 T		03-04-2002
			CZ	20013326 A3		12-12-2001
			EE	200100484 A		16-12-2002
			WO	0055141 A1		21-09-2000
			EP	1163227 A1		19-12-2001
			HU	0201832 A2		28-12-2002
			JP	2002539199 T		19-11-2002
			NO	20014487 A		14-09-2001
			NZ	514706 A		28-11-2003
			PL	350522 A1		16-12-2002
			SK	13032001 A3		04-06-2002
			TR	200102782 T2		22-04-2002
			US	2002177601 A1		28-11-2002
			ZA	200107185 A		21-06-2002
WO 9813354	A	02-04-1998	AT	228114 T		15-12-2002
			AU	729968 B2		15-02-2001
			AU	4561397 A		17-04-1998
			BR	9711302 A		17-08-1999
			CA	2263319 A1		02-04-1998
			CN	1231662 A ,C		13-10-1999
			CZ	9901039 A3		16-06-1999
			DE	69717294 D1		02-01-2003
			DE	69717294 T2		04-09-2003
			DK	929530 T3		24-02-2003
			EP	0929530 A1		21-07-1999
			ES	2185999 T3		01-05-2003
			WO	9813354 A1		02-04-1998
			HK	1019332 A1		05-09-2003
			IL	129038 A		10-11-2002
			JP	3438818 B2		18-08-2003
			JP	2001500891 T		23-01-2001
			JP	2003238539 A		27-08-2003
			JP	2004002406 A		08-01-2004
			KR	2000048572 A		25-07-2000
			NO	991422 A		24-03-1999
			NZ	334014 A		27-10-2000
			PL	332385 A1		13-09-1999
			PT	929530 T		31-03-2003
			RU	2198879 C2		20-02-2003
			SI	929530 T1		30-04-2003
			SK	38999 A3		08-10-1999
			TR	9900674 T2		21-07-1999
			TW	520364 B		11-02-2003
			US	2002173646 A1		21-11-2002
			US	6414148 B1		02-07-2002
			ZA	9708553 A		25-03-1998
			HU	9902850 A2		28-04-2000
WO 0051991	A	08-09-2000	DE	19908567 A1		31-08-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/003915

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0051991	A		DE 19911366 A1 DE 19928306 A1 DE 19954816 A1 AU 3281600 A BG 105765 A BR 0008524 A CA 2361174 A1 CN 1341104 T CZ 20013079 A3 EE 200100449 A WO 0051991 A1 EP 1157011 A1 HR 20010617 A1 HU 0301132 A2 ID 29800 A JP 2002538145 A NO 20014114 A NZ 513802 A PL 351619 A1 SK 12112001 A3 TR 200102505 T2 ZA 200105983 A	21-09-2000 28-12-2000 17-05-2001 21-09-2000 29-03-2002 18-12-2001 08-09-2000 20-03-2002 14-11-2001 16-12-2002 08-09-2000 28-11-2001 31-10-2002 29-12-2003 11-10-2001 12-11-2002 15-10-2001 28-09-2001 19-05-2003 03-12-2001 21-01-2003 20-09-2002
WO 9730035	A 21-08-1997	AT AU AU BR CA CN CZ DE DE DK EP ES WO HK HU IL JP NO NZ PL PT SI SK TR TW US ZA RU	237596 T 719434 B2 1729097 A 9707495 A 2242425 A1 1211239 A ,B 9802535 A3 69720965 D1 69720965 T2 880508 T3 0880508 A1 2194181 T3 9730035 A1 1016607 A1 9901155 A2 125686 A 2000504714 T 983687 A 330868 A 328310 A1 880508 T 880508 T1 108798 A3 9801530 T2 581765 B 6184225 B1 9701180 A 2196137 C2	15-05-2003 11-05-2000 02-09-1997 27-07-1999 21-08-1997 17-03-1999 11-11-1998 22-05-2003 05-02-2004 30-06-2003 02-12-1998 16-11-2003 21-08-1997 26-09-2003 28-07-1999 10-11-2002 18-04-2000 13-08-1998 28-01-2000 18-01-1999 31-07-2003 31-10-2003 11-01-1999 23-11-1998 01-04-2004 06-02-2001 13-08-1997 10-01-2003